FDA Briefing Document

Joint Pulmonary-Allergy Drugs Advisory Committee

and

Drug Safety and Risk Management Advisory Committee Meeting

December 10, 2015

The safety of codeine in children 18 years of age and younger

Disclaimer Statement

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the issue of the safety of codeine sulfate for the relief of pain or cough in pediatric patients to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Table of Contents

FDA Summary Memorandum

Date: November 12, 2015

From: Sally Seymour, MD
Deputy Director for Safety, Division of Pulmonary, Allergy, and Rheumatology Products

Judy Racoosin, MD, MPH
Deputy Director for Safety, Division of Anesthesia, Analgesia, and Addiction Products

David Moeny, R.Ph., MPH
Deputy Director, Division of Epidemiology II
Office of Surveillance and Epidemiology

Valerie Pratt, MD
Deputy Director for Safety, Division of Nonprescription Drug Products

To: Members, Pulmonary Allergy Drugs and Drug Safety and Risk Management Advisory Committees

Subject: The safety of codeine in children 18 years of age and younger

1. Introduction

Thank you for your participation in the Joint Pulmonary Allergy Drugs and Drug Safety and Risk Management Advisory Committee (PADAC/DSaRM) meeting to be held on December 10, 2015. As participants in this Advisory Committee (AC) meeting, you provide important expert scientific advice and recommendations to the US Food and Drug Administration (FDA) on the regulatory decision making process related to drugs marketed in the United States. The upcoming meeting is to discuss the safety of codeine in children 18 years of age and younger.

Codeine sulfate is an opioid indicated for the relief of mild to moderately severe pain where the use of an opioid analgesic is appropriate. Codeine for analgesia is marketed as single ingredient codeine or most often in combination with acetaminophen. Codeine is also indicated for the relief of cough and is available in combination with other medications in prescription products for cough and symptoms associated with upper respiratory allergies or common cold. Codeine is also available through the over the counter (OTC) Drug Monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products

(21 CFR 341.14, 21 CFR 341.74, 21 CFR341.90) in combination with other medications for cough and cold symptoms.

Codeine is partially metabolized to morphine, its most potent analgesic metabolite, through the CYP2D6 pathway. A high degree of variability exists for CYP2D6 metabolism of codeine because of underlying genetic differences in CYP2D6 activity. Because of this variability, depending on CYP2D6 activity, patients may be at risk for therapeutic failure or at risk for toxicity.

Given the variability in the metabolism of codeine, the safety of codeine use in children has been a concern for years, particularly the risk of respiratory depression and death. Over the past decade, FDA has updated the label for codeine-containing products regarding the risk of respiratory depression. In 2007, prescription codeine labels were updated with information regarding variable metabolism and the risk of respiratory depression, specifically in infants of nursing mothers who used codeine. In 2012, FDA issued a Drug Safety Communication about reports of death and respiratory depression in pediatric patients, primarily with use of codeine following tonsillectomy and/or adenoidectomy. In February 2013, after completing a review of the available safety data, FDA required a Boxed Warning and Contraindication for the use of codeine in this setting.[1] In June 2013, following a review of the relevant data, the European Medicines Agency (EMA) made the determination that "codeine-containing products indicated in the management of pain should only be indicated in children above 12 years of age and contraindicated in paediatric patients below 18 years of age undergoing tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome as well as in women during breast-feeding and in patients known to be CYP2D6 ultra-rapid metabolisers."

In April 2015, the (EMA) completed a review of the use of codeine for cough and cold indications. The EMA contraindicated the use of codeine in children below 12 years of age for cough and cold and recommended that codeine not be used in children and adolescents 12-18 years who have breathing problems.[2]

Given the continued concern with use of codeine in children, the Agency convened this AC meeting to discuss the available safety data with codeine use in children for cough or analgesia and to obtain input on whether the use of codeine in children should be restricted further beyond the current Contraindication and whether codeine should be available as an antitussive through the OTC Drug Monograph. Given that the FDA has made a determination about the efficacy of these products, the efficacy of codeine for analgesia and cough will not be addressed in the FDA Briefing Document or presentation. The focus of the meeting is safety.

The FDA Briefing Document includes the following:

1. Summary Memorandum that provides background and regulatory history for this safety issue as well as a summary of FDA's reviews;
2. Draft Points to Consider or topics for discussion at the upcoming meeting;
3. FDA Summary Memo for the 2012-2013 Codeine Safety Review
4. FDA 2013 Drug Safety Communication for Codeine

5. Racoosin JA, Roberson DW, Pacanowski MA, and Nielsen DR. New Evidence about an Old Drug – Risk with Codeine after Adenotonsillectomy. *N Engl J Medicine 2013;* 368:2155-2157.
6. Office of Clinical Pharmacology (OCP) 2012 review on the clinical pharmacology and pharmacogenomics of codeine and a 2015 addendum;
7. Office of Surveillance and Epidemiology (OSE) review of post-marketing safety reports, data on emergency room visits for codeine events, relevant literature, and data on codeine utilization in the US;
8. EMA Pharmacovigilance Assessment Committee (PRAC) June 2013 Assessment Report for codeine-containing medicinal products indicated in the management of pain in children
9. EMA Pharmacovigilance Assessment Committee (PRAC) March 2015 Report on codeine use in children for cough and cold
10. EMA April 2015 Recommendations for codeine use in children for cough and cold
11. Overview of FDA Monograph for Codeine

At the meeting, you will be asked to discuss the safety of codeine for use in the treatment of pain or cough in pediatric patients. Again, we are grateful for your participation in this meeting and thank you for providing your expertise and insight. We are hopeful that the discussion at this meeting will assist us in determining possible regulatory options, including, but not limited to, changes to the product labeling.

2. Clinical Pharmacology

Codeine is a prodrug that is metabolized by the CYP2D6 pathway. Approximately 5-10% of codeine is converted to morphine by CYP2D6, which is in turn metabolized to the glucuronide metabolites via UGT2B7, as shown in the figure below.

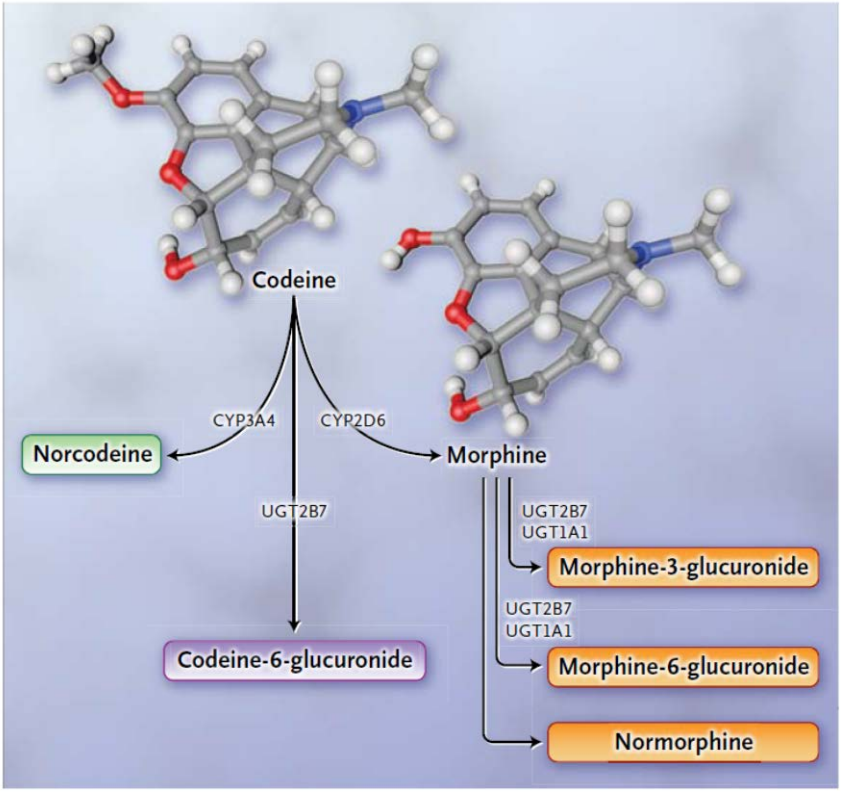


Figure 1. Codeine Metabolism

Source: *N Engl J Med* 2013: 368 (23): 2155-2157. Adapted from Crews KR, Gaedigk A, Dunnenberger HM, et al. *Clinical Pharmacology & Therapeutics* 2012; 91:321-6.

A high degree of variability exists for CYP2D6-mediated activation of codeine because of underlying genetic differences in CYP2D6 activity. Patients may be classified as having one of four metabolic phenotypes depending on the number of active genes the patient has, as shown in the table below.

Table 1. Pharmacogenomic Variations for CYP2D6

Predicted phenotype	Prevalence*	Genotypes	Examples of diplotypes
Ultrarapid metabolizer (UM)	~1–2%†	An individual carrying more than two copies of functional alleles	**1/*1xN, *1/*2xN*
Extensive metabolizer (EM)	~77–92%	An individual carrying two alleles encoding full or reduced function or one full function allele together with either one nonfunctional or one reduced-function allele	**1/*1, *1/*2, *2/*2, *1/*41, *1/*4, *2/*5, *10/*10*
Intermediate metabolizer (IM)	~2–11%	An individual carrying one reduced and one nonfunctional allele	**4/*10, *5/*41*
Poor metabolizer (PM)	~5–10%	An individual carrying no functional alleles	**4/*4, *4/*5, *5/*5, *4/*6*
* Frequency data are for Caucasians. Frequencies may differ substantially by race/ethnicity † Ultrarapid metabolizer frequencies are as follows: African Americans, 3%; Arab, 16-28%; Caucasian, 1-10%; Chinese, 0.5-1%; Ethiopian, 16-28%; Hispanic, 0.5-1%; Japanese, 0.5-1%; North African, 16-28%			

Source: Adapted from Crews KR, Gaedigk A, Dunnenberger HM, et al. *Clinical Pharmacology & Therapeutics* 2012; 91:321-6.

Patients with CYP2D6 dysfunction may have therapeutic failure secondary to reduced biotransformation of codeine to morphine. Conversely, UMs may be at risk of toxicity because of more rapid and complete conversion to morphine. For example, Sindrup, et al. evaluated oral codeine (75 mg) in 12 EMs and 12 PMs identified using urinary sparteine metabolic ratios to study plasma concentrations and therapeutic response.[3] The authors found that morphine was undetectable in PMs (< 4 nM) and peak morphine concentrations were between 4.9–37.6 nM in EMs. In the EM group, codeine significantly decreased the pain threshold caused by laser stimuli, whereas no significant analgesic effects were observed in the PM group.

In a separate study, a single 50-mg dose of oral codeine led to a 20-fold higher AUC of morphine and M6-glucuronide in 8 EMs as compared to 6 PMs.[4] Individuals with the UM phenotype are at the highest risk for morphine exposure and toxicity, including respiratory depression. The codeine AUC and the Cmax were not significantly different in UMs compared to EMs, although the morphine AUC was 45.5% higher in UMs ($p<0.05$). [5] When examining outcomes, significantly more adverse effects were reported in the UM group compared with the EMs, suggesting that risk for codeine toxicity is dependent on morphine exposure. The clinical and pharmacokinetic literature has been extensively reviewed by the Clinical Pharmacogenetics Implementation Consortium.[6]

For a more detailed discussion of the clinical pharmacology and pharmacogenomics of codeine, refer to the review by the Office of Clinical Pharmacology.

3. Background

Codeine is an opioid that is a derivative of opium and a selective mu receptor agonist that has been available in the US since the 1950s. Codeine is currently approved as both an analgesic agent and as an antitussive. Dihydrocodeine is an ingredient in some headache treatments, but those products are not approved in children, and they will not be a topic of discussion at the advisory committee meeting.

A. Codeine for analgesia

Codeine is available as a single ingredient product and in combination with other medications (primarily acetaminophen) for the relief of mild to moderately severe pain. Single ingredient codeine products are not approved for use in children less than 18 years of age; however, codeine/acetaminophen combination products are labeled for pediatric use with dosing instructions down to three years of age. Table 2 shows the available prescription codeine products for analgesia indications and the relevant pediatric labeling.

Table 2. Available Prescription Codeine Products for Analgesia Indications

Application	Product	Dosage Form	Pediatric Labeling
NDA 22402 202245 (Roxane)	Codeine sulfate	Tablet Solution	Boxed Warning regarding deaths related to ultra-rapid metabolism of codeine to morphine Contraindication for postoperative pain management in children post tonsillectomy and/or adenoidectomy (T&A) Safety and effectiveness and PK in children < 18 years of age have not been established.
ANDAs (multiple)	Codeine phosphate and acetaminophen*	Tablet Solution	Boxed Warning regarding deaths related to ultra-rapid metabolism of codeine to morphine Contraindication for postoperative pain management in children post T&A Safe dosage of acetaminophen and codeine phosphate oral solution has not been established in pediatric patients below the age of 3 years.
NDA 11483	Synalgos DC (Dihydrocodeine, aspirin, caffeine)	Capsule	Preparations containing aspirin should be kept out of the reach of children. Synalgos-DC is not recommended for patients 12 years of age and under. Since there is no experience in children who have received this drug, safety and efficacy in children have not been established. Modifications to the Pediatric Use section to highlight the risk of respiratory depression and death in children who are undergoing tonsillectomy and/or adenoidectomy
ANDA 204785	Dihydrocodeine, acetaminophen, caffeine*	Capsule	Safety and effectiveness of acetaminophen, caffeine, and dihydrocodeine bitartrate capsules in pediatric patients have not been established. The Usage in Children section includes the class-wide statement about the risk of respiratory depression and death in children who are undergoing tonsillectomy and/or adenoidectomy

Source: FDA Orange Book search on September 30, 2015
* Product labels also contain a Boxed Warning for hepatotoxicity related to acetaminophen.

B. Codeine for cough (prescription)

Codeine sulfate is indicated for the relief of cough and is available with a prescription in combination with other medications for cough and symptoms associated with upper respiratory allergies or the common cold. Table 3 shows the available prescription codeine products for cough/cold indications and the relevant pediatric labeling.

Table 3. Available Prescription Codeine Products for Cough/Cold Indications

Application	Product	Dosage Form	Relevant Pediatric Labeling
NDA 206323 (Spriaso)	Chlorpheniramine maleate; codeine phosphate	Extended Release Oral Tablet	Not indicated for patients <18 years; Boxed Warning regarding deaths related to ultra-rapid metabolism of codeine to morphine Contraindication for postoperative pain management in children post T&A
NDA 207768 (Tris Pharma)	Chlorpheniramine polistirex; codeine polistirex (Tuzistra XR)	Extended Release Oral Suspension	
NDA 8306 ANDA (multiple)	Codeine phosphate; phenylephrine hydrochloride; promethazine hydrochloride	Oral Syrup	Contraindication in children < 6 yrs; Boxed Warning regarding respiratory depression in children (promethazine/codeine combo) Boxed Warning regarding deaths related to ultra-rapid metabolism of codeine to morphine Contraindication for postoperative pain management in children post T&A Dosing information for children: • 12 years and older: 10 mg every 4 to 6 hours; NTE 60 mg in 24 hours • 6 to <12 years: 5 to 10 mg every 4 to 6 hours; NTE 60 mg in 24 hours
NDA 8306 ANDA (multiple)	Codeine phosphate; promethazine hydrochloride	Oral Syrup	
ANDA 88704 (Sti Pharma)	Codeine phosphate; pseudoephedrine hydrochloride; triprolidine hydrochloride (Triacin C)	Oral Syrup	Boxed Warning regarding deaths related to ultra-rapid metabolism of codeine to morphine Contraindication for postoperative pain management in children post T&A Dosing information for children: • 12 years and older: 20 mg every 4 to 6 hours; NTE 80 mg in 24 hours • 6 to <12 years: 10 mg every 4 to 6 hours; NTE 40 mg in 24 hours • 2 to <6 years: 5 mg every 4 to 6 hours, NTE 10 mg
Source: FDA Orange Book search on June 4, 2015			

Combinations of codeine with promethazine were first approved in 1952 (NDA 8306), and were later the subject of a Drug Efficacy Study Implementation (DESI) review (DESI 6514). After reformulation in 1984, they were found effective as an antihistamine antitussive combination, with or without a decongestant. Promethazine is a phenothiazine derivative that acts as an H_1 receptor antagonist, sedative, antiemetic, and antitussive. Because of the potential for respiratory depression, promethazine product labels have a Boxed Warning for use in pediatric patients less than 2 years of age, along with a caution for use in pediatric patients 2 years of age and older. Combination promethazine and

codeine product labels currently contain a Boxed Warning for respiratory depression and a Contraindication in patients less than 6 years of age.

In addition to the Boxed Warning on promethazine and codeine combination products, all the approved codeine-containing products have a Boxed Warning regarding deaths related to ultra-rapid metabolism of codeine to morphine and a Contraindication for postoperative pain management in children post tonsillectomy and/or adenoidectomy.

As shown above in Table 3, some older codeine cough/cold combination products have dosing information for children as young as 2 years of age and other products for children as young as 6 years of age (e.g., promethazine and codeine products), whereas the newer approved codeine combination products do not currently have dosing information for children.

C. Codeine for cough (OTC)

Codeine is also available through the OTC Drug Monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (21 CFR 341.14, 21 CFR 341.74, 21 CFR 341.90) in combination with other medications for cough and cold symptoms. An OTC drug monograph describes the conditions for marketing for certain OTC drugs that are generally recognized as safe and effective (GRASE) if they meet the conditions of 21 CFR 330.1 and each of the conditions contained in the specific monograph. The conditions in 21 CFR 330.1 include, among other things, requirements that the product be unadulterated, be in compliance with current good manufacturing practices, and that it not be misbranded. If manufacturers comply with the conditions in the monograph, they may market an OTC product under the monograph without going through the FDA New Drug Application (NDA) review process.

21 CFR Part 341 is the monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use. The majority of the OTC medications for cold, cough, and allergy symptoms are brought to market under this monograph. Codeine, codeine phosphate, and codeine sulfate are listed as antitussive active ingredients in 21 CFR 341.14(a)(2). It is important to note that these codeine ingredients may be used only in combination with at least one nonnarcotic active ingredient (e.g. antihistamine and/or decongestant and/or analgesic/antipyretic) as stated in 21 CFR 290.2 and 21 CFR 1308.15, which also limits the concentration of codeine in such combinations and requires that the nonnarcotic ingredient confer "valuable medicinal qualities other than those possessed by codeine alone." The limits for codeine are:

- Not more than 200 milligrams of codeine per 100 milliliters or per 100 grams.
- Not more than 100 milligrams of dihydrocodeine per 100 milliliters or per 100 grams.

Also, FDA issued a final rule on February 1, 2002 (67 FR 4904) to amend regulations regarding certain label statements on prescription drugs. 21 CFR 290.1 was added to make clear the agency's determination that a controlled substance in Schedules II-V of the

Controlled Substance Act must be dispensed by prescription only unless otherwise determined by the Agency. 21 CFR 290.2 was added to allow the exemption for small amounts defined as not more than 200 milligrams of codeine per 100 milliliters or per 100 grams.

The OTC monograph for codeine includes labeling for children down to 6 years of age (21 CFR 341.74(d)(1)(ii)) and includes professional labeling for children down to 2 years of age (21 CFR3 41.90). Relevant labeling for codeine is highlighted below:

OTC monograph requirements for the "Directions" section of the Drug Facts Label:

For products containing codeine ingredients identified in 21 CFR 341.14(a)(2), labeling is outlined in 21 CFR 341.74

- Adults and children 12 years of age and over: 10 to 20 milligrams every 4 to 6 hours, not to exceed 120 milligrams in 24 hours, or as directed by a doctor.
- Children 6 to under 12 years of age: Oral dosage is 5 to 10 milligrams every 4 to 6 hours, not to exceed 60 milligrams in 24 hours, or as directed by a doctor.
- Children under 6 years of age: Consult a doctor. A special measuring device should be used to give an accurate dose of this product to children under 6 years of age.
- Giving a higher dose than recommended by a doctor could result in serious side effects for your child.

OTC monograph requirements for the "Warnings" section of the Drug Facts Label:

For oral and topical antitussives

- "A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur, or is accompanied by fever, rash, or persistent headache, consult a doctor."

For oral and topical antitussives labeled for adults or for adults and children under 12 years of age

- "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor."

For products containing codeine ingredients identified in 21 CFR 341.14(a)(2)

- "May cause or aggravate constipation."

For products containing codeine ingredients identified in 21 CFR 341.14(a)(2) when labeled for use in adults and children under 12 years of age

- "Adults and children who have a chronic pulmonary disease or shortness of breath, or children who are taking other drugs, should not take this product unless directed by a doctor."

OTC monograph requirements for professional labeling (provided to health professionals but not the general public)

- Children 2 to under 6 years of age: 1 milligram per kilogram body weight per day administered in four equal divided doses. The average body weight for each age may also be used to determine dosage as follows:
    - children 2 years of age (average body weight, 12 kilograms), the dosage is 3 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours;
    - children 3 years of age (average body weight, 14 kilograms), the dosage is 3.5 milligrams every 4 to 6 hours, not to exceed 14 milligrams in 24 hours;
    - children 4 years of age (average body weight, 16 kilograms), the dosage is 4 milligrams every 4 to 6 hours, not to exceed 16 milligrams in 24 hours:
    - children 5 years of age (average body weight, 18 kilograms), the dosage is 4.5 milligrams every 4 to 6 hours, not to exceed 18 milligrams in 24 hours.
- The manufacturer must relate these dosages for its specific product dosages for its specific product to the use of the calibrated measuring device discussed in paragraph (c)(3) of this section. If age is used to determine the dose, the directions must include instructions to reduce the dose for low-weight children.
- Parents should be instructed to obtain and use a calibrated measuring device for administering the drug to the child, to use extreme care in measuring the dosage, and not exceed the recommended daily dosage.
- A dispensing device (such as a dropper calibrated for age or weight) should be dispensed along with the product when it is intended for use in children 2 to under 6 years of age to prevent possible overdose due to improper measuring of the dose.
- Codeine is not recommended for use in children under 2 years of age. Children under 2 years may be more susceptible to the respiratory depressant effects of codeine, including respiratory arrest, coma, and death

A 2015 review by FDA found 45 products currently registered with FDA to be marketed under the OTC monograph. Two unapproved new drug products were also found, and additional products may have been marketed previously and subsequently withdrawn, or not registered. The registered products comprise 13 distinct combinations of codeine with various other active ingredients, and were registered by 18 different companies.

Twenty-eight states and the District of Columbia permit the sale of codeine without a prescription, while 22 states and Puerto Rico prohibit the sale of codeine without a prescription.[7] Most if not all of the state laws allowing the OTC sale of codeine require the pharmacist to oversee or personally complete the transaction, and allow the pharmacist to choose not to sell the product OTC. For codeine that is sold OTC, all states require that the purchaser's identifying information and details of the sale be recorded. States differ on the maximum allowable quantity which can be purchased at one time (60 mL to 240 mL), the amount of time required before additional purchases are permitted (48 hours to 96 hours), and the minimum age of a purchaser (18 years to 21 years). The variations between states involve regulations and laws which are more restrictive than the federal requirements in 21 CFR 1306.26.

Keep in mind that while the input from this AC panel will be considered in determination of whether further labeling revisions are warranted for codeine products, the regulatory pathway for changing the labeling for the NDA/ANDA products and the monograph products is quite different. Changing labeling for the NDA/ANDA products can be

accomplished by working with the manufacturers. However, implementing labeling changes for the FDA monograph products is accomplished through a two-phase rulemaking process and would be expected to be quite lengthy in duration.

4. Recent Developments in Codeine Safety

The following is a brief summary of recent developments in codeine safety that are relevant to the discussion at the upcoming AC meeting.

- Neonatal toxicity related to exposure to high levels of morphine through the breast milk of an ultra-rapid metabolizer mother taking codeine
    - A 2006 publication in the Lancet described the death of a nursing infant who was exposed to high levels of morphine in breast milk because the mother, who was taking codeine, was an ultra-rapid metabolizer of codeine, a CYP2D6 substrate.[8]
    - In 2007, FDA revised codeine labeling to warn of this risk and also issued communications to healthcare providers and the public regarding use of codeine in nursing mothers and the risk to infants exposed to morphine in breast milk from mothers who were ultra-rapid metabolizers of codeine.[9]
- Fatal and life-threatening respiratory depression in children following codeine treatment for pain post-adenotonsillectomy who were CYP2D6 ultra-rapid metabolizers
    - Following identification of a case series published in *Pediatrics* in April 2012,[10] FDA embarked on an evaluation of the issue.
    - In August 2012, FDA issued a Drug Safety Communication acknowledging the case series about the risk of death or life-threatening respiratory depression following adenotonsillectomy in some children who received codeine for pain control following surgery, and describing that an evaluation was under way.[11]
    - In February 2013, FDA issued a Safety Labeling Change notification letter to codeine- and dihydrocodeine-containing products to require a contraindication for use in children following tonsillectomy and/or adenoidectomy and a boxed warning describing the risks of being an ultra-rapid metabolizer of codeine.[1]
    - The FDA's assessment of this safety issue was published online in April 2013 as a Perspective in the *New England Journal of Medicine* - "New Evidence about an Old Drug — Risk with Codeine after Adenotonsillectomy".[12]
    - The required labeling changes were approved in May 2013. The relevant labeling is shown below.

WARNING: DEATH RELATED TO ULTRA-RAPID METABOLISM OF CODEINE TO MORPHINE

Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism.

CONTRAINDICATION

Codeine sulfate is contraindicated for postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy.

WARNING

Death Related to Ultra-Rapid Metabolism of Codeine to Morphine

Respiratory depression and death have occurred in children who received codeine in the post-operative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 [CYP2D6] or high morphine concentrations). Deaths have also occurred in nursing infants who were exposed to high levels of morphine in breast milk because their mothers were ultra-rapid metabolizers of codeine.

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (gene duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing).

Children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine is contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy.

When prescribing codeine, healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of morphine overdose.

PEDIATRIC USE

Respiratory depression and death have occurred in children with obstructive sleep apnea who received codeine in the postoperative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). These children may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine is contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy [see Contraindications (4)].

A summary memo of the Agency's review of this safety issue from 2012-13 is included in the FDA Briefing Package.

- In October 2012, the EMA initiated a review of codeine focusing on codeine use in children for pain relief. In June 2013, the EMA Pharmacovigilance Risk Assessment Committee (PRAC) recommended the following, which was endorsed by the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh).[13]
    - Codeine-containing medicines should only be used to treat acute (short-lived) moderate pain in children above 12 years of age, and only if it cannot be relieved by other painkillers such as paracetamol [acetaminophen] or ibuprofen, because of the risk of respiratory depression associated with codeine use.
    - Codeine should not be used at all in children (aged below 18 years) who undergo surgery for the removal of the tonsils or adenoids to treat obstructive sleep apnoea, as these patients are more susceptible to respiratory problems.
    - The product information of these medicines should carry a warning that children with conditions associated with breathing problems should not use codeine.
    - The risk of side effects with codeine may also apply to adults. Codeine should therefore not be used in people of any age who are known to be ultra-rapid metabolisers nor in breastfeeding mothers (because codeine can pass to the baby through breast milk). The product information for codeine should also include general information for healthcare professionals, patients and carers on the risk of morphine side effects with codeine, and how to recognise their symptoms.

- In June 2013, Health Canada announced that it reviewed the safety of prescription pain and cough medications containing codeine and is no longer recommending their use in children less than 12 years of age. This recommendation was based on very rare cases of serious side effects and deaths in children that have been attributed to codeine, when given directly to a child, or to babies from breast milk.[14]

- In April 2014, the EMA initiated a review of codeine use in children for cough and cold. In March 2015, the PRAC recommended the following which was endorsed by CMDh.[15]

- Codeine should be contraindicated in children below 12 years. This means it must not be used in this patient group.
- Use of codeine for cough and cold is not recommended in children and adolescents between 12 and 18 years who have problems with breathing.

The EMA recommendations for restrictions regarding codeine use in children for cough and cold indications is the primary reason that the Agency decided to re-open this safety issue and convene this Advisory Committee meeting.

5. Clinical Considerations – Analgesia

Few analgesics have been studied sufficiently to support pediatric-specific labeling for efficacy or safety, but work is ongoing to attempt to fill this important clinical gap.[16] As safety concerns arose with codeine, some professional societies and scientific organizations have provided assessments or recommendations specifically about the use of codeine. These are summarized below.

American Academy of Pediatrics
The American Academy of Pediatrics (AAP) has not taken a formal position on codeine for analgesia in children.

American Academy of Otolaryngology-Head and Neck Surgery
The clinical practice guideline on tonsillectomy in children published by the American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS) in 2011 includes a discussion of post-operative pain control.[17] The guideline did not recommend prescribing specific drugs because they consider that pain "can often be managed with over-the-counter analgesics and hydration." The guideline goes on to say that "acetaminophen with codeine does not provide superior control of pain compared with acetaminophen only following tonsillectomy either at rest or with swallowing." But it also notes that in some cases acetaminophen will not provide adequate pain control. Regarding other pain management options, the guideline states that use of non-steroidal anti-inflammatory drugs (NSAIDs) has been controversial because of the known adverse effect on platelet function associated with NSAID use. They cite a Cochrane Collaboration review of 13 randomized controlled trials (including about 1000 children) that found that "NSAIDs did not significantly alter postoperative bleeding compared with placebo or other analgesics.,.", and go on to conclude that NSAIDs (except for ketorolac) "can be used safely for the postoperative treatment of pain following tonsillectomy."

Subsequently, in an editorial coauthored by the FDA and AAO-HNS about the risk associated with codeine after adentonsillectomy[11], the AAO-HNS notes that they "…supported the labeling changes [restricting codeine use in children following adenotonsilectomy] because of the increasing evidence that these extremely rare but catastrophic events can be related to codeine use, because codeine is ineffective in some patients (poor metabolizers), and because of emerging clarity that a variety of other drugs

(e.g., some nonsteroidal antiinflammatory drugs) are safe to use and do not increase the risk of bleeding."

World Health Organization
In March 2011, the World Health Organization removed codeine from the list of essential medicines for children[18] using the rationale below (excerpted from the report):

> The Committee therefore recommended the deletion of codeine from Section 2.2 of the Model List of Essential Medicines for children due to evidence indicating that the analgesic effect is low or absent in neonates and young children; evidence of considerable pharmacogenetic variability among populations, making its efficacy and safety questionable in an unpredictable proportion of the paediatric population and low quality evidence indicating that it is not safer or more efficacious than paracetamol or ibuprofen for the treatment of musculoskeletal trauma in children. The Committee also noted the need to improve access to appropriate analgesia, especially morphine, in all settings.

6. Clinical Considerations - Cough

In the past decade, the use of cough and cold medications, including codeine, has been of interest and various groups have raised concern about the treatment of cough/cold in pediatric patients as outlined below.

American Academy of Pediatrics
The American Academy of Pediatrics has taken a formal opinion on the use of codeine (and dextromethorphan [DM]) for cough. In 1997, the AAP Committee on Drugs provided recommendations on the Use of Codeine and DM-Containing Cough Remedies in Children.[19] The AAP cautioned about the lack of studies to support the efficacy and safety of narcotics or dextromethorphan as antitussives in children. The Committee noted that because of adverse effects and overdosage associated with codeine and DM products for cough, patients and parents should be educated about the lack of proven antitussive effects and the potential risks of these products. The AAP also noted that cough due to URI is short-lived and suppression of cough may be hazardous. In 2007, AAP reaffirmed the statement. [20]

American College of Chest Physicians
In 2006, the American College of Chest Physicians (ACCP) issued Guidelines for Evaluating Chronic Cough in Pediatrics.[21] In these guidelines, one of the recommendations was the following: "In children with cough, cough suppressants and other OTC cough medications should not be used as patients, especially young children, may experience significant morbidity and mortality."

EMA and Health Canada
As noted in the section above, both Health Canada and EMA have made recommendations to not use codeine pain and cough medications in children less than 12 years of age.

Food and Drug Administration

The following FDA activities are included for completeness, although the focus of these activities was on OTC cough and cold products rather than on codeine.

In March 2007, FDA received a Citizen's Petition regarding OTC cough/cold medications regarding concerns that the products have not been shown to be safe and effective for the treatment of cough and cold in children under 6 years of age.

In response to the Citizen's Petition, FDA convened a Joint Nonprescription Drugs Advisory Committee and Pediatric Advisory Committee in October 2007 to discuss the safety and efficacy of OTC cough and cold products for pediatric use. The available efficacy and safety data for OTC cough and cold medications and extrapolation were topics for discussion; however, codeine products were not a focus of the discussion. At that time the committee voted that antihistamines, nasal decongestants, and antitussives should not be used for the common cold in the following age groups:

- Less than 2 years of age – Yes: 21, No 1, Abstain: 0
- 2 to 6 years of age – Yes: 13, No 9, Abstain: 0
- 6 to 12 years of age – Yes: 7, No 15, Abstain: 0

Based upon the Advisory Committee recommendations and the Agency's review, FDA issued a press release in January 2008, recommending that OTC cough/cold medicines not be used in children younger than 2 years of age.[22] The Agency did not make any formal recommendation about the use of these products in children older than 2 years. In October 2008, the Consumer Healthcare Products Association (CHPA) announced voluntary actions by its members to modify product labels of OTC cough/cold medicines to state "do not use" in children under 4 years of age.[23]

Approved Non-Codeine Containing Antitussive Medications

Because the committee is being tasked with providing recommendations on the use of codeine for cough in pediatric patients, information about alternative products available for the treatment of cough in pediatric patients is summarized briefly. Antitussive non-codeine containing medications that are approved for the treatment of cough, including both prescription and OTC products, are shown in Table 4 on the following page.

With regard to prescription antitussive agents, there are two approved active ingredients, benzonatate and hydrocodone. Benzonatate (Tessalon, NDA 11210, and generics) is a local anesthetic that acts peripherally by anesthetizing and dampening the activity of the stretch receptors located in the respiratory passages, lungs, and pleura. It is available as an oral capsule, and has labeling regarding the risk of severe hypersensitivity reactions, including bronchospasm, laryngospasm and cardiovascular collapse, if the capsule is sucked or chewed. Therefore, benzonatate use is limited to children 10 years of age and older who can swallow the capsule without holding it in their mouths or chewing on it. Hydrocodone (Hycodan, NDA 05213) was first approved in 1942. While Hycodan, an immediate-release product, is now discontinued, generics to it are available. Like codeine, hydrocodone is a centrally acting opioid antitussive that is available in as a single ingredient (with homatropine) or combination with other cough/cold medications. Unlike

codeine, hydrocodone is not metabolized by the CYP2D6 pathway to morphine. Nevertheless, hydrocodone can cause respiratory depression, which can be fatal in younger children. As a result, the hydrocodone antitussive products have information in the product labeling about respiratory depression in children less than 6 years of age.

With regard to non-prescription antitussive agents, there are several non-narcotic alternative agents listed in the OTC Monograph, including chlophedianol, dextromethorphan, diphenhydramine, and topical agents. Many dextromethorphan-containing products are available OTC. Dextromethorphan does not carry the same risk of respiratory depression as either codeine or hydrocodone. Diphenhydramine-containing products are also available; however, diphenhydramine does carry the risk of sedation as well as paradoxical excitatory activity, particularly in younger children. Finally, topical agents (menthol and camphor) are available in several formulations; however, topical agents are most often used in lozenge form, which is not appropriate for younger children. Further, camphor is absorbed through the skin and is toxic if taken internally, so its use as an antitussive is limited.

Table 4. Approved Non-Codeine Containing Antitussive Medications

Active Ingredient (product name)	Class	Age	Relevant Labeling
Prescription Products			
Benzonatate (Tessalon and generics)	Peripheral Anesthetic	≥10 years	• Do not break, chew, crush • Temporary local anesthesia • Accidental ingestion resulting in death has been reported in children <10 years of age • Dosing information for children 10 years and older
Hydrocodone + homatropine (Hycodan and generics) + chlorpheniramine (Tussionex)	Centrally acting opioid	≥6 years	• Tussionex: Contraindicated for use in patients less than 6 years of age because use is associated with cases of fatal respiratory depression • Hycodan: Warning about respiratory depression in patients less than 6 years of age • Use with caution in children 6 years of age and older
Hydrocodone + chlorpheniramine (Vituz) + pseudoephedrine (Rezira) + chlorpheniramine and pseudoephedrine (Zutripro) + guaifenesin (Obredon, Flowtuss) + guaifenesin, pseudoephedrine (Hycofenix)	Centrally acting opioid	≥18 years	• Not indicated for pediatric patients under 18 years of age • Warning regarding respiratory depression, including fatalities in children less than 6 years of age
Over-the-Counter Antitussive Products (FDA monograph 21 CFR341.14)			
Chlophedianol Hydrochloride	Centrally acting	≥6 years	• Non-narcotic for temporary relief of cough • Do not take for chronic cough • Children under 6 years of age: Consult

Active Ingredient (product name)	Class	Age	Relevant Labeling
			a doctor • OTC Monograph also contains professional labeling for dosing in children 2 to <6 years of age
Dextromethorphan and Dextromethorphan hydrobromide	Centrally acting	≥2 years	• Non-narcotic for temporary relief of cough • Do not take for chronic cough • Children under 2 years of age: Consult a doctor
Diphenhydramine citrate and Diphenhydramine hydrochloride	Antihistamine /antitussive	≥6 years	• Non-narcotic for temporary relief of cough • May cause marked drowsiness • Alcohol, sedatives, and tranquilizers may increase sedative effect • Do not give to children less than 12 years of age who have a breathing problem • Children under 6 years of age: Consult a doctor • OTC Monograph also contains professional labeling for dosing in children 2to <6 years of age
Camphor and Menthol	Topical (ointment, lozenge, steam inhalation)	≥2 years	• Topical: For external use only • Flammability: Safety concern about fire-related events when ointment vehicle or alcohol-based solutions are placed in hot water or heated in the microwave • Children under 2 years of age: Consult a doctor

7. Safety Review (FAERS and Literature)

The Division of Pharmacovigilance I (DPV-I) in the Office of Surveillance and Epidemiology (OSE) completed a review of codeine and respiratory depression in pediatric patients. OSE also completed a review in 2012 that focused on cases with codeine in children with fatal outcomes. The most recent review for this AC meeting is a cumulative review of all serious cases of respiratory depression for all codeine-containing products, and there is overlap of identified death cases that were previously discussed in the 2012 FDA Drug Safety Communication (and in the 2012-13 Summary Review) in which the FDA warns of the risk that codeine use in certain children after tonsillectomy and/or adenoidectomy may lead to rare, but life-threatening adverse events or death.

DPV-I searched the FDA Adverse Event Reporting System (FAERS) database for reports of cases of respiratory depression with codeine-containing products with a serious outcome in children 18 years and younger. Details of the search strategy are described in the OSE Review (Table 1 in OSE Review). The FAERS search identified 64 serious respiratory

depression cases, from 1965 to 2015, in pediatric patients who had used a codeine-containing product. Descriptive characteristics of the FAERS cases are shown in Table 5.

The majority (n=50) of the 64 cases were in patients under 12 years old. There were 24 deaths, 21 hospitalizations, and 16 life threatening cases in the series. Twenty-one of the death cases involved children less than 12 years old. Twelve of the 21 deaths in patients under 12 years old occurred when a codeine-containing product was used unrelated to tonsillectomy or adenoidectomy. The indications for codeine in these 12 cases were the following:

- cough and cold (n=7),
- general pain (n=2),
- postoperative pain not associated with tonsillectomy and/or adenoidectomy (n=2), and
- sore/strep throat pain (n=1).

Since the FDA issued the Drug Safety Communication regarding the risk in patients post tonsillectomy and/or adenoidectomy in August 2012, only one case was reported in this setting. Refer to the OSE Review for details of this case.

Among the 48 cases that reported reason for use, 34 reported pain management and 14 reported cough and cold management. The most frequently reported codeine-containing product was acetaminophen with codeine (n= 26). Promethazine with codeine (with [n=5] and without phenylephrine [n=5]) was the most frequently reported codeine-containing product in the cough and cold setting.

A temporal relationship was observed with the events occurring as early as after one dose of a codeine-containing product. Only 10 cases noted CYP2D6 genotype, so the information is limited. The OSE review includes details, including narratives for some cases.

Table 5. Descriptive characteristics of serious pediatric FAERS cases of respiratory depression reported with codeine-containing products, received by FDA as of May 26, 2015

Characteristics (N = 64)		
Sex	Male Female Unknown	35 24 5
Age (years)	Mean Median Range 0-1 year 2-5 years 6-11 years 12-18 years	6 2.9 0.03 – 17.21 16 23 11 14
Country	United States Foreign	41 23
Initial FDA Received	1969-2012	42

Characteristics (N = 64)		
Year*	2013	9
	2014	11
	2015	2
Event Year*	1969-2012	33
	2013	4
	2014	1
	Unknown	26
Report Type	Expedited	44
	Direct	16
	Periodic	4
Time to event onset from start of therapy	Median	5 doses
	Range	1-18 doses
	1 dose	10
	2 doses	5
	3 doses	4
	4 doses	3
	6 doses	3
	10 doses	1
	12 doses	3
	18 doses	2
	Unknown	33
Codeine-Containing Products†	Acetaminophen with codeine	26
	Codeine unspecified	23
	Promethazine, phenylephrine with codeine	5
	Promethazine with codeine	5
	Guaifenesin with codeine	2
	Chlorpheniramine, phenylephrine with dihydrocodeine	1
	Triprolidine, pseudoephedrine with codeine	1
	Aspirin with codeine	1
	Dihydrocodeine unspecified	1
Serious Outcomes‡	Death	24
	Cough and cold use	7
	Post tonsillectomy and/or adenoidectomy	7
	General pain	2
	Other postoperative pain	2
	Sore throat/tonsillitis pain	2
	Dental pain	1
	Unknown use	3
	Hospitalization	21
	Life-threatening	16
	Disability	2
	Other Serious	30
Preferred Terms (Top 10)	Respiratory Depression	13
	Apnoea	9
	Dyspnoea	9
	Unresponsive to Stimuli	8
	Death	7
	Pyrexia	7

Characteristics (N = 64)		
	Toxicity to Various Agents	7
	Loss of Consciousness	6
	Vomiting	6
	Cyanosis	5
	Overdose	5
Reasons for Use	Pain	34
	Post tonsillectomy and/or adenoidectomy	17
	Other surgery	5
	General pain	7
	Sore throat/Tonsillitis	3
	Dental pain	2
	Unknown	16
	Cough and Cold	14
Mention of CYP2D6 Genotype	Without mention	54
	With mention	10
	Ultra-rapid metabolizer (UM)	7
	Extensive metabolizer (EM)	3
Codeine or morphine levels (n=15) §	Above therapeutic range	13
	Blood levels	2
	Postmortem	11
	Therapeutic range	2
	Blood levels	1
	Postmortem	1

* Reports received prior to the DSC issued by the FDA in 2012 were grouped together.
† Cases may contain more than one codeine-containing product.
‡ Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. Reports may include multiple outcomes.
§ There was one FAERS literature case that did not contain levels within the report; however, levels were obtained from the literature article.

OSE also conducted a literature search which identified 3 additional case reports of death in children 4-10 years of age associated with codeine-containing products in different clinical settings. These cases are briefly summarized here with more details in Section 3.3.1.1 and 3.3.2.1 of the OSE Review:

- 10-year-old overweight Guatemalan female 5 days status post orthopedic surgery found un-responsive following treatment with acetaminophen with codeine (2 doses) and diazepam (1 dose). Postmortem codeine and morphine blood concentrations were in the toxic range.

- 4-year-old obese female status post tonsillectomy/adenoidectomy discharged home with acetaminophen with codeine every 4 hours for pain. She received a total of 4 doses at 4-hour intervals, went to bed, and was found unresponsive the following morning. Resuscitative measures were unsuccessful. CYP2D6 testing found the patient to have an extensive metabolizer (normal) phenotype.

- 6-year-old overweight female was prescribed guaifenesin with codeine for severe cough and respiratory infection. She received a total of 3 doses throughout the day and was noted by her mother to be a "little bit blue" after her last dose. The patient was found dead the next morning by her mother. Postmortem codeine and morphine blood concentrations were in the toxic range.

Overall, the OSE review concludes that there is some case report evidence of respiratory depression, sometimes resulting in death, following codeine-containing product use for both pain and cold/cough treatment, particularly in the pediatric population less than 12 years of age. The FAERS data cannot be used to generate reliable estimates of the incidence of life-threatening or fatal respiratory depression with the pediatric use of codeine-containing products.

8. Drug Utilization

Given that the Agency is asking the AC panel whether it recommends additional restriction of use of codeine in pediatric patients, it is important to understand how codeine is currently being used in pediatric patients in the US. The Agency's Division of Epidemiology II (DEPI-II) assessed the utilization data for codeine, and a brief overview is summarized here. The detailed utilization data is located in the OSE Review.

Figure 2 below and Table 2.3.2 in the OSE review provide the pediatric utilization of prescription codeine-containing products over time. While Figure 2 shows the data for the 0-11 and 12-18 year age group, Table 2.3.2 in the OSE review includes details on age subgroups: 0-1, 2-5, 6-11, and 12-18. Over 2010-2014, the number of pediatric patients (0-18 years old) who received dispensed prescriptions for codeine decreased 40% to about 1.9 million patients in 2014 (Figure 2), in 2014, pediatric patients accounted for 14% of all patients (13.2 million patients) who received dispensed prescriptions of codeine-containing (analgesic or cough/cold) products from U.S. retail pharmacies. Of the 1.9 million pediatric patients in 2014, 56% were under age 12 years and 45% were ages 12-18 years.[i] By drug class, 76% of pediatric patients received prescriptions for analgesic codeine-containing products and 26% of pediatric patients received prescriptions for cold/cough products in 2014 (Table 2.3.2 OSE Review).

Of the pediatric patients who received analgesic codeine-containing products, 99.6% of pediatric patients received prescriptions for analgesic codeine-acetaminophen combination products in 2014. In 2014, 52% and 42% of pediatric patients received cough/cold codeine-guaifenesin and codeine-promethazine combination products, respectively, (Table 2.3.2 OSE Review) in 2014. Primary care practitioners were the top prescriber specialties for both cough/cold and analgesic codeine-containing products (Table 2.3.3 OSE Review).

[i] Summing patients across patient age bands and time periods will result in double counting and overestimates of patient counts. Moreover, the sum of the percentages will be greater than 100% because patients are double counted across age bands.

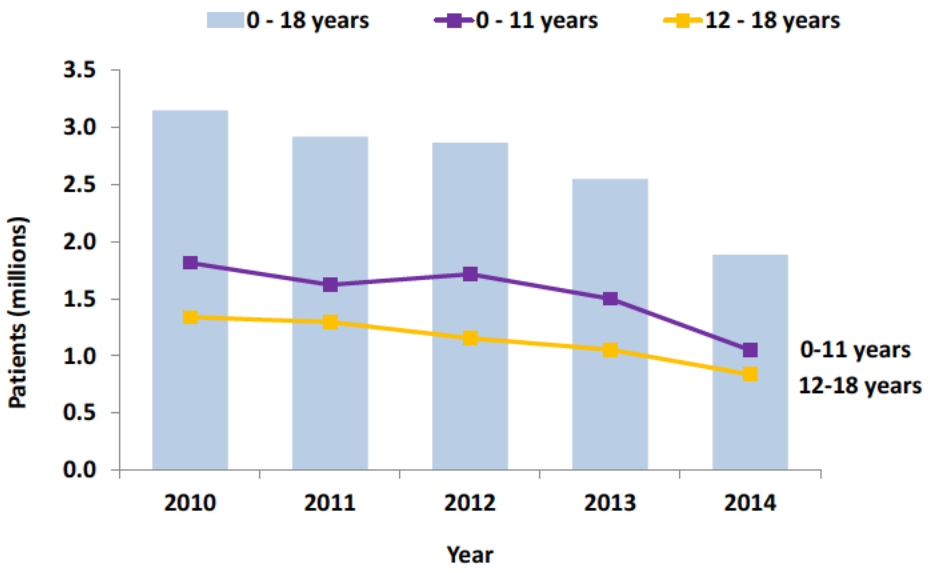


Figure 2. National estimates of <u>pediatric patients (0-18 years)</u> who received dispensed prescriptions for codeine-containing products by patient age from U.S. outpatient retail pharmacies, years 2010-2014

Source: IMS Health, Vector One®: Total Patient Tracker. Years 2010-2014. Data extracted June and August 2015.

Because codeine is available OTC, DEPI assessed the utilization of codeine-containing cough/cold products sold OTC. Compared to 2010, the U.S. retail OTC sales of codeine-containing cough/cold products decreased 85% to 169,000 bottles/packages sold in 2014 (Table 2.3.1 OSE review). Since 2012, combination codeine-guaifenesin accounted for the majority of total retail OTC sales of codeine-containing cough/cold products at 61%-100%. There is no demographic information provided for patients using OTC codeine cough/cold products because such information is not collected in the data resources available to the FDA.

9. Epidemiology Data

DEPI examined other epidemiological data sources for adverse effects from use of codeine-containing products in children. The National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project collects data (from 63 hospitals) on emergency department (ED) visits for adverse drug events (ADEs). All the cases in NEISS-CADES are ED visits for a condition that the treating clinician explicitly attributed to the use of a drug or a drug-specific effect, but exclude intentional self-harm, drug therapeutic failures, drug withdrawal, and drug abuse. Only visits by patients alive at the time of discharge from the ED are included in these data.

The NEISS-CADES data for patients age 18 years and under during the years 2004-2013 , included 73 ED visits for codeine **cough and cold** products and 261 ED visits for codeine **analgesic** products as shown in Table 6. (Note: These are counts, not national projections,

of visits from a sample of hospitals over the whole 2004-2013 period.) Accidental/unintentional ingestion and allergic reaction accounted for the majority of these codeine-related pediatric ED visits. The specific ADEs are listed in Table 4.2.3.3 in the OSE Review; although GI complaints were the most common, there were cases of dyspnea, somnolence, and altered/ depressed level of consciousness.[ii]

Table 6. NEISS-CADES 2004 – 2013: Summary of codeine-containing product-related ED visits by adverse drug event category and age group

Codeine-containing Cough and Cold Products				
Age Group	**Adverse Drug Event**			
	Accidental/ Unintentional	**Allergic Reaction**	**Adverse Effect**	**Total**
<2 years	13	1	0	14
2-5 years	19	4	3	26
6-11 years	4	6	1	11
12-18 years	4	13	5	22
Total	**40**	**24**	**9**	**73**
Codeine-containing Analgesic Products				
Age Group	**Adverse Drug Event**			
	Accidental/ Unintentional	**Allergic Reaction**	**Adverse Effect**	**Total**
<2 years	27	5	0	32
2-5 years	29	17	10	56
6-11 years	4	34	19	57
12-18 years	14	61	41	116
Total	**74**	**117**	**70**	**261**

Data from SAMHSA's Drug Abuse Warning Network (DAWN) for 2004-2011 are used to publish national annual estimates of ED visits resulting from an adverse drug reaction (ADR). This category includes ED visits in which an adverse health consequence (e.g., side effect or an allergic reaction) resulted when taking prescription drugs, OTC medications, or dietary supplements. For methodological details of DAWN, see the OSE Review.

National annual estimates of ED visits for ADRs for codeine-containing **cough and cold** products in the pediatric population were not published due to estimate imprecision from small case counts. The DAWN national estimate of ADR ED visits related to codeine/combination **analgesic** products for 2011 was 1073 for children 12-17 years (Table 7). There were not enough data for the younger age groups to estimate ED visits for 2011. The DAWN data do not provide details on the types of ADRs leading to the ED visits.

[ii] In a previous DEPI review focused on adverse reactions involving codeine use for tonsillectomy pain, 14 pediatric ED cases (in children aged 12-18 years) were identified in the 2004-2010 NEISS-CADES data.

Table 7. DAWN 2004-2011: National Estimates of Adverse Drug Reaction ED Visits associated with Codeine-containing Analgesic products, by year and pediatric age group

DAWN: 2004-2011								
Codeine/combination Analgesics	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**
0-5 years	*	*	*	*	542	853	*	*
95% Confidence Intervals					106, 979	233, 1,474		
6-11 years	*	846	822	1,207	1,060	1,342	*	*
95% Confidence Intervals		328, 1,364	120, 1,524	202, 2,213	524, 1,597	460, 2,223		
12-17 years	841	653	1,520	984	609	1,707	1,043	1,073
95% Confidence Intervals	184, 1498	145, 1,161	781, 2,259	439, 1,530	220, 998	734, 2,679	398, 1,688	123, 2,023

* indicates figure does not meet standards of precision. Estimates with a relative standard error greater than 50% or an unweighted count or estimate less than 30 are suppressed.
Source: Center for Behavioral Health Statistics and Quality, SAMHSA, Drug Abuse Warning Network, 2011.

To summarize, both NEISS-CADES (2004-2013) and DAWN (2004-2011) data show that there were ED visits associated with the use of codeine-containing products in pediatric patients.

10. Codeine as a Controlled Substance

Finally, it is important to note that codeine is a controlled substance under the Controlled Substances Act (CSA); thus, we have included information regarding the CSA and codeine. Depending on the dose of codeine and whether it is in combination with another drug, codeine products are controlled in Schedules II, III, or V of the CSA, as described below:

- Schedule II – high potential for abuse which may lead to severe psychological or physical dependence
    - codeine single ingredient products
- Schedule III – potential for abuse less than Schedules I or II and abuse may lead to moderate or low physical dependence or high psychological dependence
    - codeine ≤ 90mg per dosage unit (e.g. acetaminophen with codeine)
- Schedule V – low potential for abuse relative to substances listed in Schedule IV and consist primarily of preparations containing limited quantities of certain narcotics.
    - codeine ≤ 200mg codeine per 100 mL or per 100 grams (e.g. promethazine with codeine)

The codeine cough/cold combination preparations for discussion at this AC meeting would fall under Schedule III or V.

Under 21 CFR1306.26, a "controlled substance listed in Schedules II, III, IV, or V which is not a prescription drug as determined under the Federal Food, Drug, and Cosmetic Act, may be dispensed by a pharmacist without a prescription to a purchaser at retail, provided that:"

"(a) Such **dispensing is made only by a pharmacist** (as defined in part 1300 of this chapter), and not by a nonpharmacist employee even if under the supervision of a pharmacist (although after the pharmacist has fulfilled his professional and legal responsibilities set forth in this section, the actual cash, credit transaction, or delivery, may be completed by a nonpharmacist);

(b) **Not more than 240 cc. (8 ounces)** of any such controlled substance containing opium, nor more than 120 cc. (4 ounces) of any other such controlled substance nor more than 48 dosage units of any such controlled substance containing opium, nor more than 24 dosage units of any other such controlled substance may be dispensed at retail to the same purchaser in any given 48-hour period;

(c) The **purchaser is at least 18 years of age**;

(d) The pharmacist requires every purchaser of a controlled substance under this section not known to him to furnish suitable **identification** (including proof of age where appropriate);

(e) A **bound record book** for dispensing of controlled substances under this section is maintained by the pharmacist, which book shall contain the name and address of the purchaser, the name and quantity of controlled substance purchased, the date of each purchase, and the name or initials of the pharmacist who dispensed the substance to the purchaser (the book shall be maintained in accordance with the recordkeeping requirement of Sec. 1304.04 of this chapter); and

(f) A **prescription is not required** for distribution or dispensing of the substance pursuant to any other Federal, State or local law.

(g) Central fill pharmacies may not dispense controlled substances to a purchaser at retail pursuant to this section" *[bold emphasis added]*

11. Concluding Remarks

Codeine has been approved for use for pain or cough in pediatric patients for decades. Over time, new information about the pharmacogenomics and variability in metabolism of codeine has become available. A review of the safety data shows reports of respiratory depression and death in pediatric patients following treatment with codeine. Some reports suggest the variability in metabolism of codeine could play a role. Because of these reports, various professional societies have raised concern about the use of codeine in pediatric patient populations. Some regulatory agencies, including FDA, have taken regulatory actions to limit the use of codeine in children in certain settings. Given the continued concern with use of codeine in children, you will be asked to discuss the safety of codeine for use in the treatment of pain or cough in pediatric patients. We seek your input on whether the use of codeine in children should be restricted further beyond the current Contraindication for pain management in children post-adenotonsillectomy and whether codeine should be available as an antitussive through the OTC Drug Monograph. Thank you again for your participation in this advisory committee meeting. We look forward to the discussion.

12. Reference List

[1] February 20, 2013, FDA Drug Safety Communication [http://www.fda.gov/Drugs/DrugSafety/ucm339112.htm]

[2] Assessment report for codeine-containing medicinal product indicated in the management of pain in children. EMA/441891/2013 dated 24 June 2013.

[3] Sindrup SH, Brosen K, Bjerring P, et al. Codeine increases pain thresholds to copper vapor laser stimuli in extensive but not poor metabolizers of sparteine. *Clinical Pharmacology and Therapeutics* 1990; 48 (6): 686-693.

[4] Yue QY, Hasselstrom J, Svensson JO, Sawe J. Pharmacokinetics of codeine and its metabolites in Caucasian healthy volunteers; comparisons between extensive and poor hydroxylators of debrisoquine. *British Journal of Clinical Pharmacology* 1991; 31(6):635-642.

[5] Kirchheiner J, Schmidt H, Tzvetkov M, et al. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. *The Pharmacogenomics Journal* 2007; 7(4):257-265.

[6] Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Codeine Therapy in the context of *Cytochrome P4502D6* Genotype. *Clinical Pharmacology & Therapeutics* 2012; 91:321-6.

[7] National Association of Board of Pharmacy: The 2015 Survey of Pharmacy Law 2015; 73-77.

[8] Koren G, Cairns J, Chitayat D, et al. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet* 2006; 368(9536):704.

[9] FDA Press Release on Codeine Use by Nursing Mothers [http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108968.htm]

[10] Kelly LE, Rider M, van den Anker J, et al. More Codeine Fatalities After Tonsillectomy in North American Children. *Pediatrics* 2012; 129(5):e-1343-7.

[11] August 15, 2012, FDA Drug Safety Communication [http://www.fda.gov/Drugs/DrugSafety/ucm313631.htm]

[12] Racoosin JA, Roberson DW, Pacanowski MA, and Nielsen DR. New Evidence about and Old Drug – Risk with Codeine after Adenotonsillectomy. *N Engl J Medicine 2013;* 368: 2155-2157.

[13] European Medicines Agency: Codeine-containing medicines [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Codeine-containing_medicines/human_referral_prac_000008.jsp&mid=WC0b01ac05805c516f]

[14] Health Canada's review recommends codeine only be used in patients aged 12 and over. June 2013 http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/33915a-eng.php

[15] European Medicines Agency: Codeine-containing medicinal products for the treatment of cough or cold in paediatric patients [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Codeine_containing_medicinal_products_for_the_treatment_of_cough_and_cold_in_paediatric_patients/human_referral_prac_000039.jsp&mid=WC0b01ac05805c516f]

[16] FDA Pediatric Product Development http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/ucm049867.htm

[17] Baugh RF, Archer SM, Mitchell RB, et al. Clinical Practice Guideline: Tonsillectomy in Children. *Otolaryngology – Head and Neck Surgery* 2011; 144: S1.

[18] Unedited report of the 18th Expert Committee on the Selection and Use of Essential Medicines http://www.who.int/selection_medicines/Complete_UNEDITED_TRS_18th.pdf

[19] American Academy of Pediatrics Committee on Drugs. Use of Codeine- and Dextromethorphan-Containing Cough Remedies in Children. *Pediatrics* 1997; 99(6):918-920.

[20] American Academy of Pediatrics Policy Statement. AAP Publications Retired or Reaffirmed, October 2006. *Pediatrics* 2007; 119(2):405.

[21] Chang AB and Glomb WB. Guidelines for Evaluating Chronic Cough in Pediatrics. *Chest* 2006; 129 (1 Suppl):260S-283S.

[22] FDA Press Release January 17, 2008. FDA Releases Recommendations Regarding Use of Over-the- Counter Cough and Cold Products [http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116839.htm]

[23] Statement from CHPA on the Voluntary Label Updates to Oral TOC Children's Cough and Cold Medicines. October 7, 2008. [http://www.chpa.org/10_07_08labelupdatecoughmedicine.aspx]

Draft Points to Consider

1. **Discussion**: Discuss the available data on the safety of codeine use for cough in pediatric patients. Please address the following age groups in your discussion: <6 years of age, <12 years of age, <18 years of age.

2. **Discussion**: Discuss the available data on the safety of codeine use for pain in pediatric patients. Please address the following age groups in your discussion: <6 years of age, <12 years of age, <18 years of age.

3. **Voting:** Based upon your discussion of the available safety data with codeine, do you think that the current contraindication for codeine (for pain management in the post tonsillectomy and adenoidectomy setting) should be expanded to a contraindication for codeine for use for any pain management in children?

   As per 21 CFR 201.57c(5), a drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit. Only known hazards, and not theoretical possibilities, can be the basis for a contraindication.

   a. If yes, provide your recommendation for the age for the contraindication (e.g. <6 years, <12 years, <18 years) and the rationale for your recommendation.
   b. If no, provide your rationale and any other recommendation you may have.

4. **Voting:** Based upon your discussion of the available safety data with codeine, do you think that codeine should be contraindicated for the treatment of cough in children? (**Yes or No**)

   As per 21 CFR 201.57c(5), a drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit. Only known hazards, and not theoretical possibilities, can be the basis for a contraindication.

   a. If yes, provide your recommendation for the age for the contraindication (e.g. <6 years, <12 years, <18 years) and the rationale for your recommendation.
   b. If no, provide your rationale and any other recommendations you may have.

5. **Voting:** Based upon your discussion of the available safety data with codeine, do you think that codeine should be available through the FDA monograph over the counter (21CFR341.1; 21CFR341.90) for the treatment of cough in children? (**Yes or No**)

   a. If yes, provide your recommendation for the age for availability (e.g. ≥ 6 years, ≥ 12 years, ≥ 18 years), the rationale for your recommendation, and any specific labeling recommendations.

b. If no, provide your rationale and any other recommendations you may have.

Tracked Safety Issue (TSI) Integrated Review Memorandum

Division of Anethesia, Analgesia, and Addiction Products
Office of Drug Evaluation 2
Center for Drug Evaluation and Research
Food and Drug Administration

NDA/BLA	*NDAs: 22-402; 202-245* *ANDAs: 40119; 85861; 85883; 86024; 87006; 87508; 89450; 91238*
Drug name	*Codeine*
TSI #	*1319*
TSI open (create) date	*May 3, 2012*
Safety Issue Name	*Death/respiratory arrest in children who are ultrarapid metabolizers of CYP2D6 substrates*
Author name	*Judith A. Racoosin, MD, MPH*
Date	*October 31, 2012*

I. OVERALL ASSESSMENT AND RECOMMENDATION(S)

Codeine sulfate is an opioid analgesic indicated for the relief of mild to moderately severe pain where the use of an opioid analgesic is appropriate. It is metabolized primarily to morphine by the cytochrome P450 isoenzyme CYP2D6. Polymorphisms of CYP2D6 result in some people being ultra-rapid metabolizers (UM) of CYP2D6 substrates. There are published case reports of children who underwent adenotonsillectomy to treat obstructive sleep apnea syndrome (OSAS) and died or had life-threatening respiratory depression following treatment in the postoperative period with a codeine-containing product. The children all had evidence of ultra-rapid metabolism of codeine either by genotyping or inferred from high blood morphine levels. Although the possibility exists that children who are UMs would be at risk taking codeine in any setting, the only well-documented cases come from children with OSAS who underwent adenotonsillectomy. Routine genotyping is not being recommended for several reasons: genotyping may be of limited value because some cases were extensive metabolizers, not UMs; the positive predictive value of the test is likely to be low, thus the number needed to screen in order to prevent one event is very high; and genotyping may be difficult to implement because preoperative lab tests are not routinely obtained before adenotonsillectomy. A boxed warning will be added to labeling describing that deaths have occurred in children with obstructive sleep apnea who have evidence of being ultra-rapid metabolizers of CYP2D6 and who received codeine following tonsillectomy and/or adenoidectomy. The Warnings/Precautions, Pediatric, and Patient counseling sections of labeling will also be updated to warn of this risk. An initial Drug Safety Communication (DSC) has already been issued, and a follow-up DSC will describe the labeling changes. Consideration will be given to recommending treatment alternatives to codeine in the post-adenotonsillectomy setting.

II. BACKGROUND

Codeine sulfate is an opioid analgesic indicated for the relief of mild to moderately severe pain where the use of an opioid analgesic is appropriate. It was first approved in 1950. Two NDAs (one tablet, one oral solution) were approved in 2009 as single ingredient products (they were previously marketed unapproved products); there are eight approved ANDA products that are acetaminophen/codeine phosphate combinations.

In two recent articles in the medical literature[1,2], three deaths and one case of severe respiratory depression were reported in children who received codeine after undergoing tonsillectomy and/or adenoidectomy for obstructive sleep apnea syndrome (OSAS). The children ranged in age from two to five years old. The three deaths occurred in children who had evidence of being ultra-rapid metabolizers of substrates of the cytochrome P450 isoenzyme 2D6 (including codeine), and the life-threatening case occurred in a child who was an extensive metabolizer. All children received doses of codeine that were within the typical dose range. In these cases, signs of morphine toxicity developed within one to two days after starting codeine. The post-mortem morphine concentrations in the three children who died were substantially higher than the typical therapeutic range.[3]

A TSI was created for this safety issue because it has the potential to limit the use of codeine in a specific population and has the potential to result in labeling additions or modification to Warnings/Precautions and other sections of labeling. Furthermore, it meets the regulatory definition of a serious adverse event, and there is credible evidence that the safety issue could be associated with the drug. The TSI was deemed "priority" because it has a serious outcome (i.e., death), it involves a vulnerable population, and there is biological plausibility.

III. SIGNIFICANT REVIEW FINDINGS

Materials reviewed:

Office	Topic	Date (final DARRTS signoff)
OSE/DPV	Pediatric Deaths and Overdose with Codeine	8/9/12
OSE/DPV	Pediatric Deaths and Overdose with immediate release morphine, oxycodone, and hydrocodone	10/10/12
OSE/DEPI	NEISS-CADES search: Death or overdose in	10/2/12

[1] Ciszkowski C, Madadi P, Phillips MS, Lauwers AE, Koren G. Codeine, ultrarapid-metabolism genotype, and postoperative death. N Engl J Med 2009;361:827-8.
[2] Kelly LE, Rieder M, van den Anker J, Malkin B, Ross C, Neely MN, et al. More codeine fatalities after tonsillectomy in North American children. Pediatrics 2012;129:e1343-7.
[3] Williams DG, Patel A, Howard RF. Pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability. Br J Anaesth 2002;89:839-45.

	children with recent codeine treatment	
OCP/Pharmacogenomics	TSI for reports of codeine-related death/hospitalization in CYP2D6 ultra-rapid metabolizers	10/5/12
OSE/Drug Use	Drug Utilization Analysis for Codeine/Acetaminophen and Codeine in Pediatric Patients	8/1/12
OSE/Drug Use	Drug Utilization Analysis for Morphine Sulfate Immediate-Release (IR) in Pediatric Patients	10/25/12

The safety issues team (SIT) determined that the evaluation of the TSI should include an AERS review to identify additional cases and a drug utilization review to determine how immediate release opioids were being used in the pediatric population. The Pharmacogenomics team in the Office of Clinical Pharmacology was also asked to evaluate the issue and consider how genomic testing might be used.

OSE review: Unexplained Pediatric Deaths and Overdose with Codeine or Immediate-Release Formulations of Morphine, Oxycodone, or Hydrocodone

The AERS search spanned 1969-May 1, 2012. Codeine was searched as the active ingredient, and the MedDRA search terms included the outcome “death” and the High Level Terms “overdoses”, “death”, and “sudden death.” The search was limited to children 0-17 years old. Intentional overdoses were excluded from consideration. The table below summarizes the identified cases.

Select AERS cases: deaths and overdoses received by FDA from 1969-5/1/2012* (N=13)		
	Death (n=4) and OD (n=3) with mention of CYP2D6	**Death (n=6) without mention of CYP2D6**
Age (n=13)	Mean: 3.5 YR Median: 3 YR	Mean: 7.5 YR Median: 3 YR
Gender	Male (6) Female (1)	Male (2) Female (3) Unknown (1)
Report year	2007 (1) 2010 (2) 2012 (4)	2003 (1) 2005 (1) 2006 (1) 2010 (2) Unknown (1)
Country of occurrence	United States (1) Foreign (2) Unknown (4)	United States (4) Foreign (1) Unknown (1)
Report type	Expedited (7) Literature(7)	Expedited (6) Literature (none)
Outcome[1]	Death (4) Hospitalized (3)	Death (6)
Indications	Pain post AT (5), Cough (2)	Pain post AT (3), Oral Aphthae (1) Cough (1), Unknown (1)
Dose	Range (Death): 0.3-1mg/kg/dose; (N=4) mean: 0.65mg/kg/dose Range (OD): 0.9-1.75mg/kg/dose; (N=3) mean: 1.1mg/kg/dose	Range: 0.4-1 mg/kg/dose; (N=3) mean: 0.6mg/kg/dose Unknown dose (N=3)
Time to onset (n=11)	Mean: 38 hours Median: 2 days Range: 12-72 hours (N=6)	Mean: 39 hours Median: 48 hours Range: 1-48 hours (N=5)

[1] Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events. A report may have one or more (>1) outcome.

All seven cases that mentioned CYP2D6 metabolizer status were published cases reports. They included the four cases summarized above in the background section. Additionally there was a 29 month old male who underwent elective adenotonsillectomy for recurrent tonsillitis and 'mild to moderate sleep apnea/hypopnea' and experienced a respiratory arrest on postoperative day 2 after being treated with an acetaminophen/codeine combination product.[4] The child was resuscitated and discharged on postoperative day 13; he was found to have an EM genotype. The other two patients were twin 3 year old boys who were being treated with codeine "10 drops a day" for cough with fever[5]. One child was found unresponsive and was resuscitated; the other child was found dead. Both were genotyped as EMs. Although this was not described in the OSE review, the publication described an analysis of the content of codeine in the drops that had been administered to the twins, and concluded that the children may have been accidentally overdosed owing to the variability in the size of the drops. Notably, the time to event was lengthier (6 days) in this case than the time to event in the other cases (about 2 days).

The AERS review identified six cases of death following codeine administration that did not mention a CYP2D6 genotype. Two deaths occurred in children following adenotonsillectomy; one case was in a 9 year old boy, and the other case occurred in a 5 year old girl with a chromosomal disorder who was taking valproic acid. It was reported that the child had high levels of morphine, codeine, and acetaminophen in her blood. Another death occurred in a 2 year old boy with an unspecified medical history but

[4] Voronov P, Przybylo HJ, Jagannathan N Apnea in a child after oral codeine: a genetic variant - an ultra-rapid metabolizer. Paediatr Anaesth 2007; 17(7):684-7.
[5] Hermanns-Clausen M, Weinmann W, Auwärter V, et al. Drug dosing error with drops: severe clinical course ofcodeine intoxication in twins. Eur J Pediatr 2009;168(7):819-24.

receiving longstanding valproic acid treatment who was being treated with codeine for oral aphthae. Toxicological results showed high levels of codeine and morphine in postmortem plasma samples. A fourth death occurred in a hospitalized child who was receiving valproic acid and codeine for an unknown indication. The other two deaths occurred in children receiving codeine for cough or sore throat.

The OSE review concluded that "these cases suggest that codeine overdose leading to respiratory depression and death can occur even with approved doses of codeine. Although most of these cases were reported in the setting of adenotonsillectomy and respiratory tract infection, this risk is likely to extend to the pediatric population receiving codeine in other clinical settings." The OSE recommendations are listed below:

- Revise the Warnings section of labeling for all products containing codeine to include **overdose leading to death** has occurred in children who are ultra-rapid metabolizers of codeine expressing a specific CYP2D6 genotype.
- Issue a Drug Safety Communication and a Dear Healthcare Provider letter to communicate the potential risk of overdose and death in children who are prescribed codeine-containing products, especially those with altered CYP2D6 metabolism. It would also be prudent within these communications to advise providers to follow the FDA labeled recommended doses of 0.5 mg/kg/dose in patients over 3 years of age.
- Seek consultation from CDER's pharmacogenomics group on the utility of genetic screening tests to prospectively identify patients who may be ultra-metabolizers.

During the TSI mid-cycle meeting on August 8, 2012, the SIT decided that it would be beneficial to know if any cases of death or overdose had been reported to AERS related to the therapeutic use of immediate release morphine, oxycodone, or hydrocodone. An AERS search was conducted on August 27, 2012 using the same search strategy that was used for codeine, as described above. The search identified a foreign literature case that described a 14 year old boy who was admitted to the hospital for dehydration and treatment of tonsillitis unresponsive to oral antibiotics. He was treated with IV antibiotics, paracetamol, and morphine for pain relief. He was found unresponsive some time after a 10 mg IV dose of morphine, and was not able to be resuscitated. Death was attributed to upper airway obstruction from marked enlargement of the tonsils in the setting of infectious mononucleosis. The literature review conducted as part of this consult identified one additional relevant case report. The case report described a 5 year old child who was inadvertently administered an overdose of hydrocodone for a respiratory tract infection. In addition to the overdose, a genotype analysis demonstrated the child to be a CYP2D6 poor metabolizer resulting in a decreased ability to metabolize the hydrocodone. Furthermore, the child was taking clarithromycin which inhibits CYP3A4, another enzyme which metabolizes hydrocodone. Finally, the child was also taking valproic acid which inhibits glucuronidation of hydromorphone, the CYP2D6 metabolite of hydrocodone. All of these factors combined to make it difficult for the child to metabolize the inadvertent overdose. The DPV review concluded that "review of the medical literature and the AERS database did not recover robust cases of unexplainable or unconfounded death or opioid toxicity following use of oxycodone, hydrocodone, or morphine in pediatric patients."

NEISS-CADES Search: Identify cases of death or overdose among children who had recent treatment with codeine

The National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance Project is a national stratified probability sample of 63 hospitals with a 24 hour emergency department (ED) in the US. All case definitions are related to an ED visit for a condition that the treating physician explicitly attributed to the use of a drug or drug-specific effect. The search identified 216 cases of ED visits relate to codeine exposure. Two cases described unresponsive persons who ingested a medication containing codeine. The case summaries are excerpted from the DEPI review.

CASE 1

Age: 12

Sex: Female

Reason for ED visit: Found unresponsive

Diagnosis (*MeDRA Terms*): Unresponsive to stimuli, respiratory arrest

Suspected medications: Oxcarbazepine, Tylenol #3 (acetaminophen 300mg + codeine 30mg)

Description (*verbatim from data*): [patient] had tonsillectomy & sent home, found unresponsive with angina respirations, on pain meds, diagnosis respiratory arrest, narcotic overdose accidental. Patient received chest x-ray and head CT, was intubated and given versed, fentayl, and bicarb in ER. Admitted to the hospital – no further treatment details are available.

CASE 2

Age: 17

Sex: Female

Reason for ED visit: Unresponsive

Diagnosis (*MeDRA Terms*): Accidental exposure, coma

Suspected medications: Tylenol #3 (acetaminophen 300mg + codeine 30mg)

Description (*verbatim from data*): Found unresponsive with head down on desk at school, had taken 2 Tylenol #3 for pain due to wisdom teeth coming in. Child had been told by mother that it was ok to take the two Tylenol #3. Patient treated and released from ER – no further details regarding treatment or recovery are available.

The first case is not dissimilar from other post-adenotonsillectomy cases that have been described in publications and in AERS reports. However, there is no information regarding CYP2D6 metabolizer status.

Other sources of cases

Due to the small numbers of cases identified by the AERS and medical literature searches, we sought out other potential sources of cases. A specific goal was to determine if death or life-threatening respiratory depression had occurred with pediatric codeine use outside the post-adenotonsillectomy setting.

Conversation with Dr. Gideon Koren

Dr. Koren, Director of the Motherisk Program and Professor of Pediatrics, Pharmacology, Pharmacy, Medicine, and Medical Genetics at the University of Toronto, was the senior author on the two publications mentioned in the background section of this document. We had a teleconference with Dr. Koren on August 24, 2012 (b) (4)

(b) (4)

American Academy of Otolaryngology-Head and Neck Surgery member survey

A few days after the Drug Safety Communication posting on August 15, 2012, a CDRH otolaryngologist, Dr. Eric Mann, was contacted by Dr. Julie Goldman, a member of the Patient Safety and Quality Improvement Committee of the American Academy of Otolaryngology-Head and Neck Surgery regarding the results of a survey of physician membership that requested information about bad outcomes following tonsillectomy, such as death or permanent disability. The results of survey are in press, but summary data was shared regarding cases related to narcotics.

- 8 pediatric cases were classified as being related to narcotic medications
  - Indication: obstructive sleep apnea (7), chronic tonsillitis (1)
  - Underlying condition: Down's syndrome (3), neurologic disorder (1)
  - Outcome: deaths (7), anoxic brain injury (1)
  - CYP2D6 ultra-rapid metabolizer status: suspected due to high morphine levels (1), confirmed in post-mortem exam (1)

There is limited information about these cases, but they are not inconsistent with other post-adenotonsillectomy cases of death or life-threatening overdose following codeine ingestion that have been reported in the literature and to AERS.

Discussions with pediatric clinical pharmacologists

Dr. Gil Burckart, Associate Director for Regulatory Policy in the Office of Clinical Pharmacology, contacted some pediatric clinical pharmacologist colleagues for potential leads on identifying additional cases, including Michael Neely, M.D. from University of Southern California, Edward Krenzelok, Pharm.D., Director, Pittsburgh Poison Center, and John van den Anker, MD, PhD from Children's National Medical Center. The conversation with Dr. van den Anker resulted in a discussion that included Dr. Maryann Mazer as well. Dr. Mazer, a medical toxicologist on staff at a local poison control center, offered to search the National Poison Data System (NPDS; a database maintained by the American Association of Poison Control Centers) to look for potential cases of death or unintentional overdose related to codeine. Dr. Mazer conducted preliminary searches in NPDS to determine if there were cases of adverse events associated with pediatric codeine exposures. Looking over past five years in children up to age 6, only 2-3 cases were identified as AEs. Because of the low number of cases, and the potential difficulty of getting detailed case information, no further investigation of NPDS was conducted.

Discussion with CDER dentists

We contacted Drs. Fred Hyman and John Kelsey, medical officers/dentists in the Division of Dermatology and Dental Products to see whether they were aware of bad outcomes occurring following pediatric codeine use after dental procedures. They were not aware of specific cases; however, they provided us with the guidelines that were put forth earlier this year by the American Academy of Pediatric Dentistry regarding pediatric pain management. The guideline raises the concern about codeine metabolism due to CYP2D6 polymorphisms and suggests that healthcare professionals consider non-opioid analgesics as first line agents for post-operative pain management.

Additional literature review

During the writing of this CDTL memo, I came across a reference in the publication by Voronov (footnote 4) that described a similar case in an adult. The patient was a 66 year old man with a history of chronic lymphocytic leukemia on chronic valproic acid for a seizure disorder who was hospitalized with hypoxia and found to have a bilateral pneumonia. He was treated with ceftriaxone, clarithromycin, and voriconazole, and given codeine for his cough. On hospital day 4, he was found unresponsive. He responded to naloxone treatment with dramatic improvement in his level of consciousness, and required treatment with a naloxone drip for a period of time to maintain consciousness. Genotyping revealed him to be an ultrarapid metabolizer of CYP2D6.[6]

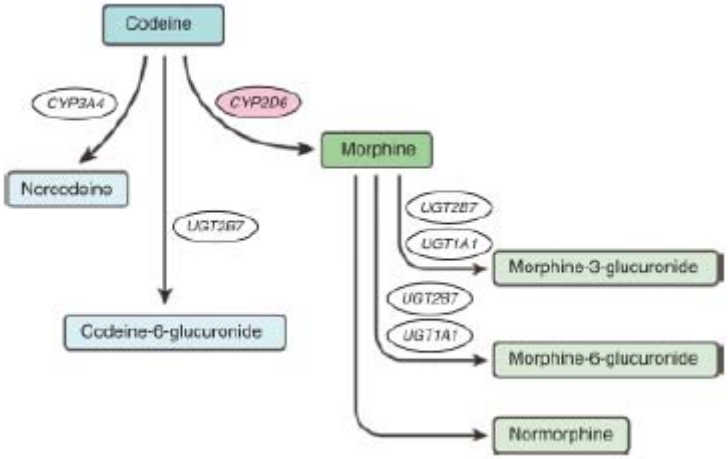
This case demonstrates that the risk of codeine intoxication related to being an ultrarapid metabolizer of CYP2D6 is not limited to children. However, it is similar to the pediatric cases in that the patient had a compromised respiratory system related to his pneumonia.

[6] Gasche Y, Daali Y, Fathi M, et al. Codeine Intoxication Associated with Ultrarapid CYP2D6 Metabolism. NEJM 2004; 351(27): 2827-31.

In this specific case, the patient's situation may have also been adversely affected by concomitant treatment with CYP3A4 inhibitors (e.g., clarithromycin, voriconazole), such that he was completely dependent on the CYP2D6 metabolic pathway.

Pharmacogenomics Review

As described in Dr. Jeremiah Momper's review, the following figure shows the codeine metabolic pathway.



Codeine is converted to morphine by CYP2D6, which is subsequently metabolized to the active moiety "M6-glucuronide" via UGT2B7. Because of genetic differences in CYP2D6 activity, there is variability in the activation of codeine. The following table excerpted from the pharmacogenomics review shows the phenotypes associated with CYP2D6 function.

CYP2D6 genotype-derived phenotype frequency and definition

Predicted phenotype	Prevalence*	Genotypes	Examples of diplotypes
Ultrarapid metabolizer (UM)	~1–2%†	An individual carrying more than two copies of functional alleles	**1/*1xN, *1/*2xN*
Extensive metabolizer (EM)	~77–92%	An individual carrying two alleles encoding full or reduced function or one full function allele together with either one nonfunctional or one reduced-function allele	**1/*1, *1/*2, *2/*2, *1/*41, *1/*4, *2/*5, *10/*10*
Intermediate metabolizer (IM)	~2–11%	An individual carrying one reduced and one nonfunctional allele	**4/*10, *5/*41*
Poor metabolizer (PM)	~5–10%	An individual carrying no functional alleles	**4/*4, *4/*5, *5/*5, *4/*6*
* Frequency data are for Caucasians. Frequencies may differ substantially by race/ethnicity † Ultrarapid metabolizer frequencies are as follows: African Americans, 3%; Arab, 16-28%; Caucasian, 1-10%; Chinese, 0.5-1%; Ethiopian, 16-28%; Hispanic, 0.5-1%; Japanese, 0.5-1%; North African, 16-28%			

As described in the review, "Individuals with the UM phenotype are at the highest risk for morphine exposure and toxicity, including respiratory depression. The codeine AUC and the C_{max} were not significantly different in UMs compared to EMs, although morphine AUC was 45.5% higher in UMs ($p<0.05$)[7]. When examining outcomes, significantly more adverse effects were reported in the UM group compared with the EMs, suggesting that risk for codeine toxicity is dependent on morphine exposure."

Dr. Momper summarized the five cases of death/overdose from the literature that occurred in children post-adenotonsillectomy. He also reviewed the evidence for efficacy of alternatives to codeine for treatment of pain in children. Finally, he discussed the potential clinical utility of CYP2D6 genotyping in this setting. Dr. Momper concluded that for the following reasons, CYP2D6 genotyping in this setting is not recommended:

- Genotyping may be of limited value because some cases were EMs, not UMs
- The positive predictive value of the test is likely to be low, thus the number needed to screen in order to prevent one event is very high
- Genotyping may be difficult to implement because preoperative lab tests are not routinely obtained before adenotonsillectomy

The pharmacogenomics review made the following labeling recommendation, "The labeling for codeine products should be revised to advise prescribers about the risk for severe outcomes in children who receive codeine for pain management following

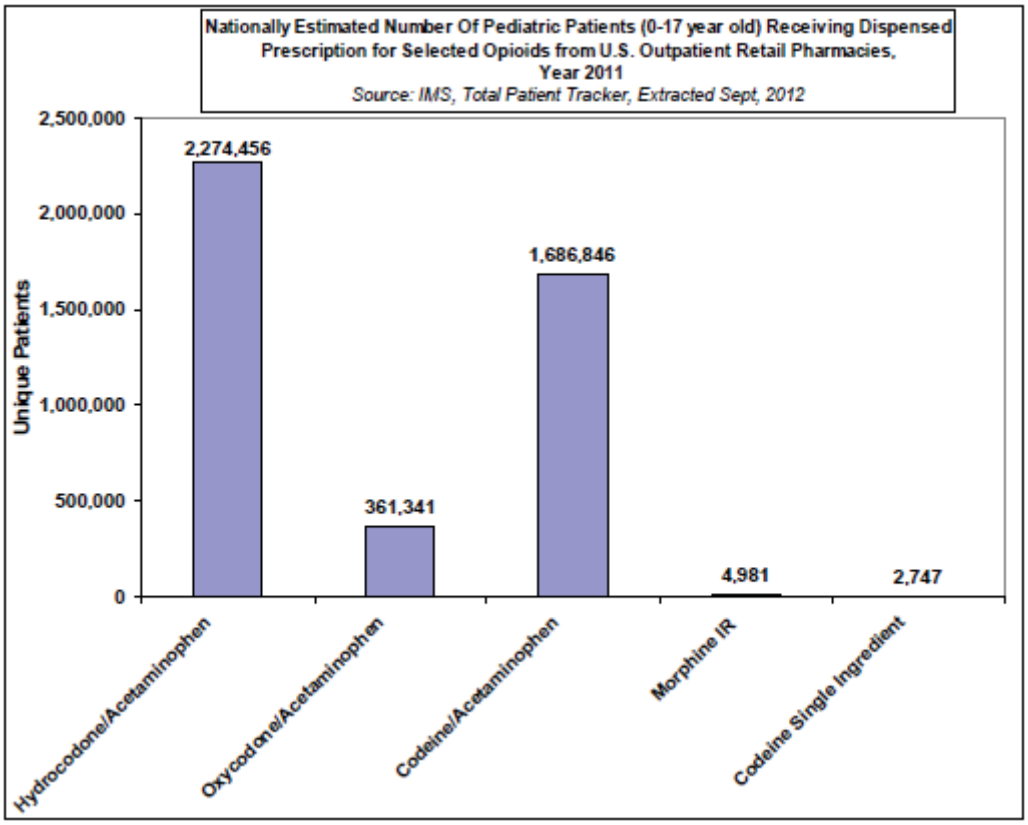
[7] Kirchheiner J, Schmidt H, Tzvetkov M, et al. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. *The pharmacogenomics journal.* Aug 2007;7(4):257-265.

tonsillectomy and/or adenoidectomy, and that use of codeine should be avoided in this patient population, regardless of genotype. If codeine must be used in children, regardless of the indication, labeling should indicate that it be administered at the lowest approved dose for the shortest duration on an as-needed basis."

Drug Utilization Reviews

We sought to better understand how codeine-containing products and potential alternative opioid therapies were being used in the pediatric population. We requested the drug utilization team in OSE to provide outpatient retail pharmacy drug utilization patterns for combination codeine/acetaminophen and single-ingredient codeine sulfate products and comparator drug products, hydrocodone/acetaminophen and oxycodone/acetaminophen, stratified by patient age (0-1 year, 2-5 years, 6-10 years, 11-17 years, and 18 years old and above) from year 2007 through year 2011, annually. A follow-up consult requested inclusion of data for immediate-release morphine, as well.

The figure below depicts the number of children (aged 0-17) who received a dispensed prescription for acetaminophen/codeine combination, single ingredient codeine, or other opioid comparators in 2011. Use of acetaminophen/codeine combination was second only to acetaminophen/hydrocodone. Use of single ingredient codeine was uncommon.



The case reports of death or life-threatening overdose with codeine occurred primarily in the 2-5 year old age range. Use of acetaminophen/codeine, single ingredient codeine, and comparators are shown in the table below, stratified by age groups. The rows highlighted

in blue show the total number of patients (all ages). The rows highlighted in grey show the 2-5 year old age group. Acetaminophen/codeine combination products were the most commonly dispensed products in this age range among the opioids evaluated.

Estimated Number of Unique Patients Receiving Dispensed Prescriptions for Oral and Liquid Combination Codeine/Acetaminophen, Single-Ingredient Codeine and comparator drugs; Hydrocodone/APAP and Oxycodone/APAP (Stratified by Age) Dispensed through U.S.Outpatient Pharmacies, Year 2007 through 2011, annually

	2007		2008		2009		2010		2011	
	Patients	Share	Patients	Share	Patients	Share	Patients	Share	Patients	Share
	N	%	N	%	N	%	N	%	N	%
Grand Total	**57,039,708**	**100.00%**	**56,349,887**	**100.00%**	**56,343,253**	**100.00%**	**60,451,127**	**100.00%**	**61,879,367**	**100.00%**
Hydrocodone/Acetaminophen	**42,387,160**	**74.31%**	**42,035,163**	**74.60%**	**41,817,958**	**74.22%**	**45,235,208**	**74.83%**	**46,453,512**	**75.07%**
0-17 years	1,929,839	4.55%	1,934,739	4.60%	1,925,665	4.60%	2,219,745	4.91%	2,274,456	4.90%
0-1 years	34,106	1.77%	35,246	1.82%	40,440	2.10%	50,567	2.28%	56,229	2.47%
2-5 years	140,092	7.26%	144,622	7.47%	169,278	8.70%	214,057	9.64%	255,479	11.23%
6-10 years	208,961	10.83%	214,891	11.11%	236,155	12.26%	283,229	12.76%	325,214	14.30%
11-17 years	1,550,116	80.32%	1,546,157	79.92%	1,504,211	78.11%	1,691,147	76.19%	1,659,034	72.94%
Oxycodone/Acetaminophen	**12,939,167**	**22.68%**	**13,112,247**	**23.27%**	**13,603,047**	**24.14%**	**14,760,528**	**24.42%**	**15,048,828**	**24.32%**
0-17 years	341,420	2.64%	350,907	2.68%	338,640	2.49%	369,098	2.50%	361,341	2.40%
0-1 years	3,310	0.97%	4,098	1.17%	3,498	1.03%	3,638	0.99%	3,522	0.97%
2-5 years	5,034	1.47%	6,490	1.85%	5,095	1.50%	5,874	1.59%	6,292	1.74%
6-10 years	10,861	3.18%	11,972	3.41%	9,677	2.86%	11,119	3.01%	11,139	3.08%
11-17 years	322,218	94.38%	328,236	93.54%	320,469	94.63%	348,451	94.41%	340,351	94.19%
Codeine/Acetaminophen	**8,619,024**	**15.11%**	**8,213,711**	**14.58%**	**7,726,912**	**13.71%**	**8,097,072**	**13.39%**	**8,294,105**	**13.40%**
0-17 years	1,910,040	22.16%	1,839,498	22.40%	1,838,697	23.80%	1,895,777	23.41%	1,686,846	20.34%
0-1 years	120,217	6.29%	114,403	6.22%	113,717	6.18%	111,987	5.91%	89,413	5.30%
2-5 years	406,434	21.28%	392,314	21.33%	419,359	22.81%	422,526	22.29%	356,662	21.14%
6-10 years	525,899	27.53%	511,111	27.79%	532,187	28.94%	533,839	28.16%	462,471	27.42%
11-17 years	862,782	45.17%	826,819	44.95%	780,140	42.43%	831,638	43.87%	781,201	46.31%
Codeine Single Ingredient	**36,013**	**0.06%**	**35,177**	**0.06%**	**35,180**	**0.06%**	**37,930**	**0.06%**	**37,512**	**0.06%**
0-17 years	2,627	7.29%	2,656	7.55%	2,547	7.24%	3,036	8.00%	2,747	7.32%
0-1 years	122	4.64%	87	3.28%	112	4.40%	168	5.52%	148	5.39%
2-5 years	339	12.90%	387	14.57%	452	17.75%	402	13.25%	279	10.17%
6-10 years	961	36.58%	920	34.64%	799	31.39%	1,108	36.49%	936	34.05%
11-17 years	1,217	46.31%	1,281	48.22%	1,190	46.73%	1,373	45.23%	1,398	50.90%

Source: IMS, Total Patient Tracker (TPT). Extracted September 2012. Source Files: TPT 2012-1267 Codeine APAP total 06-28-12.xls;TPT 2012-2002 Codeine apap 0-17 age group 09-18-12.xls; TPT 2012-1267 Codeine total 06-28-12.xls; TPT 2012-2002 codeine 0-17 age grp 09-19-12.xls; TPT_2012-1267_Hydrocodone_APAP_total_06-28-12 .xls; TPT 2012-2002 hydrocodone apap 0-17 age grp 09-18-12.xls; TPT 2012-2002 oxycodone apap 0-17 age group 09-18-12.xls; TPT 2012-1267 Oxycodone -APAP total 06-28-12.xls; TPT 2012-1267 Codeine and Compatators total 06-28-12.xls

Estimated Number of Unique Patients Receiving Dispensed Prescriptions for Morphine Sulfate IR (Stratified by Patient Age) Dispensed through U.S.Outpatient Pharmacies, Year 2007 through 2011, annually

	2007		2008		2009		2010		2011	
	Patients	Share	Patients	Share	Patients	Share	Patients	Share	Patients	Share
	N	%	N	%	N	%	N	%	N	%
Mopphine Sulfate IR	**413,181**	**100.00%**	**458,732**	**100.00%**	**446,674**	**100.00%**	**432,961**	**100.00%**	**545,633**	**100.00%**
0-17 year old	3,824	0.93%	3,687	0.80%	3,648	0.82%	4,314	1.00%	4,981	0.91%

Source: IMS, Total Patient Tracker (TPT), Extracted September 2012. Source File: TPT 2012-2002 Morphine sulfate 0-17 age 09-24-12.xls

The analysis of prescribing specialty showed that General Practice/Family Medicine/Doctor of Osteopathy was the top prescribing specialty for oral solid formulations of acetaminophen/codeine combination products and single-ingredient codeine sulfate. Otolaryngologist was the top specialty for oral liquid formulations for acetaminophen/codeine combination products, and General Practice/Family Medicine/Doctor of Osteopathy was the top prescribing specialty for oral liquid formulation of single-ingredient codeine sulfate.

The analysis of diagnosis codes associated with the use of acetaminophen/codeine combination products showed that “Surgery Follow-Up” (ICD-9 code V67.0) was the most common diagnosis code. Although not commonly mentioned, drug uses associated with “Acute Tonsillitis” (ICD-9 code 463.0) and “Chronic Disease of Tonsils and Adenoids” (ICD-9 474.0) were captured in pediatric patients. “Flu with Resp Manifest Nec” (ICD-9 code 487.1) was the most common diagnosis code associated with the use of single-ingredient codeine in pediatric patients aged 2-5 years old and 6-10 years old,

and “Chronic Sinusitis NOS” (ICD-9 code 473.9) was the only diagnosis code in pediatric patients aged 11-17 years old. Analysis of diagnosis codes for comparator drugs showed that combination hydrocodone/acetaminophen was frequently prescribed for conditions possibly related to tonsillectomy among all pediatric age groups. For combination oxycodone/acetaminophen, approximately 2% of the drug use mentions were associated with a diagnosis possibly related to tonsillectomy in the 11-17 age range, but there were no mentions in the younger children. Finally, there did not appear to be use of morphine sulfate in pediatric patients for conditions related to tonsillectomy.

IV. CONCLUSIONS

Death or life-threatening respiratory depression has occurred in children with obstructive sleep apnea syndrome (OSAS) who received codeine for postoperative pain management after adenotonsillectomy. Of the five published cases for which there is some analysis of CYP2D6 genotyping or morphine blood levels, three appeared to be ultrarapid metabolizers (UM), and two were extensive metabolizers. The AAO-HNS member survey included some suggestive cases in the post-tonsillectomy setting, but details were not available. Efforts to identify additional cases outside of the post-adenotonsillectomy setting in OSAS patients had limited success. There was one similar published case describing an adult hospitalized for pneumonia and treated with codeine for cough that led to respiratory depression and eventual recovery when he was treated with a naloxone drip; genotypic analysis showed him to be a CYP2D6 UM. A few AERS cases of unexplained death in children after codeine treatment did not include genotyping; some were confounded by intercurrent conditions. The lack of well-documented cases of death or respiratory arrest after codeine treatment in children with UM status outside of the setting of OSAS and post-adenotonsillectomy doesn’t mean that it couldn’t happen, but at this time our regulatory action will highlight that group of patients because that is what the data supports.

The concomitant use of valproic acid in some of the AERS cases and the published adult case raised the question of whether there was an additional potential drug interaction between codeine and valproic acid that was playing a role. After consultation with the Office of Clinical Pharmacology, the consensus is that valproic acid may play a minimal role inhibiting UGT-mediated clearance of morphine that is not clinically significant. Dr. Momper identified a study that specifically evaluated morphine glucuronidation in human liver microsomes and demonstrated that valproic acid only weakly inhibits morphine 3- and 6-glucuronosyltransferase activities.[8] Dr. Burckart and Dr. Yun Xu concurred with Dr. Momper’s assessment.

Planned labeling changes are described below in the “Recommended Regulatory Actions” section. Alternatives to codeine for pain management in children are not going

[8] Hara Y, Nakajima M, Miyamoto K, Yokoi T. Morphine glucuronosyltransferase activity in human liver microsomes is inhibited by a variety of drugs that are co-administered with morphine. Drug Metab Pharmacokinet 2007; 22(2):103-12.

to be described in labeling. However, some thought needs to be given to whether FDA should make such recommendations in a communication piece or published manuscript. Other groups have spoken up about the need for use of alternatives to codeine in children. An editorial entitled "It's time to rethink use of codeine in pediatric patients" was published in the AAP (American Academy of Pediatrics) News in September 2011. The author proposed morphine, oxycodone, and hydrocodone in single-ingredient liquid formulations as more predictable alternatives to morphine.[9] In 2011, the American Academy of Otolaryngology-Head and Neck Surgery published a clinical practice guideline on tonsillectomy in children.[10] The guideline cites research supporting that acetaminophen with codeine did not achieve better pain control than acetaminophen alone. The guideline also recommended that NSAIDS (with the exception of ketorolac) can be used safely for postoperative pain management. The guideline cites a review from the Cochrane Collaboration with nearly 1000 children from 13 randomized controlled trials that found that NSAIDs did not significantly alter postoperative bleeding compared with placebo or other analgesics (when ketorolac was excluded). Finally, a recent letter to the editor of the journal Pain Medicine from an anesthesiologist and otolaryngologist at Cincinnati Children's Hospital argues for the use of an opioid-free post-adenotonsillectomy pain management regimen including around-the-clock acetaminophen, daily dexamethasone, and ibuprofen (starting postoperative day 2) stating that "Despite our high volume, we have not seen any serious or life-threatening complications or an increase in incidence of inadequate pain control or increase in postoperative bleeding."[11]

The drug utilization analysis suggested that hydrocodone/acetaminophen is already being used in the 2-5 and 6-11 age range for diagnoses related to tonsillectomy. However, there is always the concern that shifting use to an opioid medication that healthcare providers are less familiar with could lead to overdose. Furthermore, hydrocodone and oxycodone are both metabolized at least in part by CYP2D6. (b) (4) That information along with the Cochrane Collaboration analysis may increase the understanding of the level of safety of NSAIDs in that setting, and ultimately, non-opioid based pain management regimens may be first choice for post-adenotonsillectomy care.

V. RECOMMENDED REGULATORY ACTION(S)

The labeling of codeine-containing products will be updated to include a boxed warning describing that respiratory depression and death has occurred in pediatric patients with OSAS following codeine treatment for post-adenotonsillectomy pain. The Warnings statement about ultra-rapid metabolizers of CYP2D6 will be moved up to the top of the section. The subsection will be renamed "Risk of death related to Ultra-Rapid Metabolism of Codeine to Morphine", and it will highlight risk of death or overdose that

[9] Galinkin JL. It's time to rethink use of codeine in pediatric patients. *AAP News* 2012; 32(9).
[10] Baugh RF, Archer SM, Mitchell RB, et al. Clinical Practice Guideline- Tonsillectomy in Children. *Otolaryngology–Head and Neck Surgery* 2011; 144(1S) S1–S30.
[11] Sadhasivam S and Myer CM. Preventing opioid-related death in children undergoing surgery. *Pain Medicine* 2012; 13: 982–983.

has occurred both in children and nursing infants (whose mothers are UMs and taking codeine). Additionally, text about pediatric deaths will be added to section 8.4 “Pediatric Use” and cautionary messages will be enhanced in section 17 “Patient counseling information.” The labeling changes will be requested through a FDAAA safety labeling change letter.

With the addition of these labeling changes, the benefits of pain management with codeine treatment still outweigh the risks associated with the drug. However, use in settings such as the disordered breathing present in children with OSAS should be discouraged.

A Drug Safety Communication was posted on August 15, 2012 along with a press release. The text of those communications is included in the Appendix to this document. The SIT determined that a follow-up DSC will be posted to alert the public to the labeling changes described above.

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

Safety review update of codeine use in children; new *Boxed Warning* and *Contraindication* on use after tonsillectomy and/or adenoidectomy

This update is in follow-up to the FDA Drug Safety Communication: Codeine use in certain children after tonsillectomy and/or adenoidectomy may lead to rare, but life-threatening adverse events or death issued on 8/15/2012.

Safety Announcement

[2-20-2013] The U.S. Food and Drug Administration (FDA) is updating the public about new actions being taken to address a known safety concern with codeine use in certain children after tonsillectomy and/or adenoidectomy (surgery to remove the tonsils and/or adenoids). Deaths have occurred post-operatively in children with obstructive sleep apnea who received codeine for pain relief following a tonsillectomy and/or adenoidectomy. Codeine is converted to morphine by the liver. These children had evidence of being ultra-rapid metabolizers of codeine, which is an inherited (genetic) ability that causes the liver to convert codeine into life-threatening or fatal amounts of morphine in the body.

A new *Boxed Warning*, FDA's strongest warning, will be added to the drug label of codeine-containing products about the risk of codeine in post-operative pain management in children following tonsillectomy and/or adenoidectomy. A *Contraindication*, which is a formal means for FDA to make a strong recommendation against use of a drug in certain patients, will be added to restrict codeine from being used in this setting. The *Warnings/Precautions*, *Pediatric Use*, and *Patient Counseling Information* sections of the drug label will also be updated.

In August 2012, FDA announced it was reviewing the safety of codeine due to cases of deaths and serious adverse events in children who took the drug after a tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine. FDA conducted a comprehensive safety review to identify additional cases of overdose or death in children taking codeine and to determine if these adverse events occurred in any other treatment settings. Many of the cases of serious adverse events or death occurred in children with obstructive sleep apnea who received codeine after a tonsillectomy and/or adenoidectomy (see Data Summary). Since these children already had underlying breathing problems, they may have been particularly sensitive to the breathing difficulties that can result when codeine is converted in the body to high levels of morphine. However, this contraindication applies to all children undergoing tonsillectomy and/or adenoidectomy because it is not easy to determine which children might be ultra-rapid metabolizers of codeine.

Health care professionals should prescribe an alternate analgesic for post-operative pain control in children who are undergoing tonsillectomy and/or adenoidectomy. Codeine should not be used for pain in children following these procedures.

For management of other types of pain in children, codeine should only be used if the benefits are anticipated to outweigh the risks.

Parents and caregivers who observe unusual sleepiness, confusion, or difficult or noisy breathing in their child should stop giving codeine and seek medical attention **immediately**, as these are signs of overdose.

Facts about codeine

- An opioid pain reliever used to treat mild to moderately severe pain
- Also used, usually in combination with other medications, to reduce coughing
- Available as a single-ingredient product or in combination with acetaminophen or aspirin and in some cough and cold medications
- In year 2011, approximately 1.7 million pediatric patients (0-17 years old) received a prescription for a codeine/acetaminophen combination product or single ingredient codeine product from U.S. outpatient retail pharmacies.[1]

Additional Information for Parents and Caregivers

- Deaths have occurred in children with obstructive sleep apnea who took codeine for pain relief after tonsillectomy and/or adenoidectomy. These children had evidence of being ultra-rapid metabolizers of codeine, which is a genetic variation that results in their liver changing codeine into morphine more rapidly and completely than other people. Ultra-rapid metabolizers are more likely to have higher-than-normal levels of morphine in their blood after taking codeine.
- Codeine should not be used to control pain in children following surgery to remove their tonsils and/or adenoids. If your child's health care professional prescribes codeine, ask for another pain medicine.
- If codeine is prescribed for other types of pain, it is often given on an "AS NEEDED" basis. Do not administer codeine to the child on a scheduled basis UNLESS the child requires the drug. Do not administer more than six (6) doses per day.
- Signs of serious side effects of codeine in children can include unusual sleepiness, confusion, and difficult or noisy breathing. **If your child shows these signs, stop giving your child codeine and seek medical attention immediately by taking your child to the emergency room or calling 911.**
- Talk to your child's health care professional if you have any questions or concerns about codeine.
- Report side effects from codeine to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- Deaths have occurred in children with obstructive sleep apnea who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a cytochrome P450 2D6 (CYP2D6) polymorphism. These children may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine.
- Routine CYP2D6 genotype testing is not being recommended for use in this setting because patients with normal metabolism may, in some cases, convert codeine to morphine at levels similar to ultra-rapid metabolizers.
- Prescribe an alternate analgesic for children who are undergoing tonsillectomy and/or adenoidectomy because codeine is now contraindicated in this setting.
- Codeine should only be used in children with other types of pain if the benefits are anticipated to outweigh the risks.
- If children are treated with codeine for other types of pain, monitor their respiratory status closely and advise parents/caregivers to monitor their children for signs of morphine overdose.
- When prescribing codeine-containing drugs, choose the lowest effective dose for the shortest period of time.
- Advise parents and caregivers to stop giving their child codeine and to seek medical attention immediately if their child is exhibiting signs of morphine overdose.
- Report adverse events involving codeine to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Data Summary

FDA conducted a comprehensive safety review of codeine use in children to identify cases of overdose or death in children taking codeine and to determine if these adverse events occur in any treatment setting. FDA first informed the public that it was reviewing the safety of codeine in children in its August 2012 Drug Safety Communication, due to cases of death and serious adverse events in children who took codeine after a tonsillectomy and/or adenoidectomy.

A search of FDA's Adverse Event Reporting System (AERS) database between 1969 to May 1, 2012 identified 13 cases of pediatric death (n=10) or overdose (n=3) associated with codeine. Seven of these cases were also described in the medical literature.[2-5] The patients ranged in age from 21 months to 9 years. Most of the cases (11/13) were reported in the setting of adenotonsillectomy (n=8) or respiratory tract infection (n=3). In most of these cases, the children appeared to receive appropriate doses of codeine. Cytochrome P450 2D6 (CYP2D6) metabolizer status was mentioned for the seven children described in the literature. Three children were characterized as ultra-rapid metabolizers, three as extensive metabolizers, and one as a likely ultra-rapid metabolizer.

FDA also sought to identify additional cases from other data sources. FDA reviewed a physician survey of mortality and major morbidity following tonsillectomy and/or

adenoidectomy conducted by the American Academy of Otolaryngology-Head and Neck Surgery. Limited information was available from these cases; however, one 3-year-old patient with obstructive sleep apnea who died after adenotonsillectomy was confirmed as being an ultra-rapid metabolizer, and one 12-year-old patient with obstructive sleep apnea who died after adenotonsillectomy was suspected of being an ultra-rapid metabolizer after high blood morphine levels were identified on autopsy.[6]

References

1. IMS Health, Total Patient Tracker (TPT). Year 2011. Data extracted January 2013.

2. Voronov P, Przybylo HJ, Jagannathan N. Apnea in a child after oral codeine: a genetic variant - an ultra-rapid metabolizer. Paediatr Anaesth 2007;17:684-7.

3. Hermanns-Clausen M, Weinmann W, Auwärter V, Ferreirós N, Trittler R, Müller C, et al. Drug dosing error with drops: severe clinical course of codeine intoxication in twins. Eur J Pediatr 2009;168:819-24.

4. Ciszkowski C, Madadi P, Phillips MS, Lauwers AE, Koren G. Codeine, ultrarapid-metabolism genotype, and postoperative death. N Engl J Med 2009;361:827-8.

5. Kelly LE, Rieder M, van den Anker J, Malkin B, Ross C, Neely MN, et al. More codeine fatalities after tonsillectomy in North American children. Pediatrics 2012;129:e1343-7.

6. Goldman JL, Baugh RF, Davies L, et al. Mortality and major morbidity after tonsillectomy: etiologic factors and strategies for prevention. Laryngoscope 2013. In press.

Racoosin JA, Roberson DW, Pacanowski MA, and Nielsen DR. New Evidence about and Old Drug – Risk with Codeine after Adenotonsillectomy. *N Engl J Medicine;* 368: 2155-2157.

http://www.nejm.org/doi/full/10.1056/NEJMp1302454

OFFICE OF CLINICAL PHARMACOLOGY

TSI	1319
NDA	22,402; 202,245
Drug Name	Codeine
Description of Submission	TSI for reports of codeine-related deaths/hospitalizations in CYP2D6 ultra-rapid metabolizers
Primary Reviewer	Jeremiah Momper, PharmD, PhD
Genomics Team Leader	Mike Pacanowski, PharmD, MPH
Associate Director for Regulatory Policy	Gilbert Burckart, PharmD
Clinical Pharmacology Team Leader	Yun Xu, PhD
OCP Division	Immediate Office, Division of Clinical Pharmacology 2
OND Division	ODEII/DAAAP
Indication(s)	Relief of mild to moderately severe pain

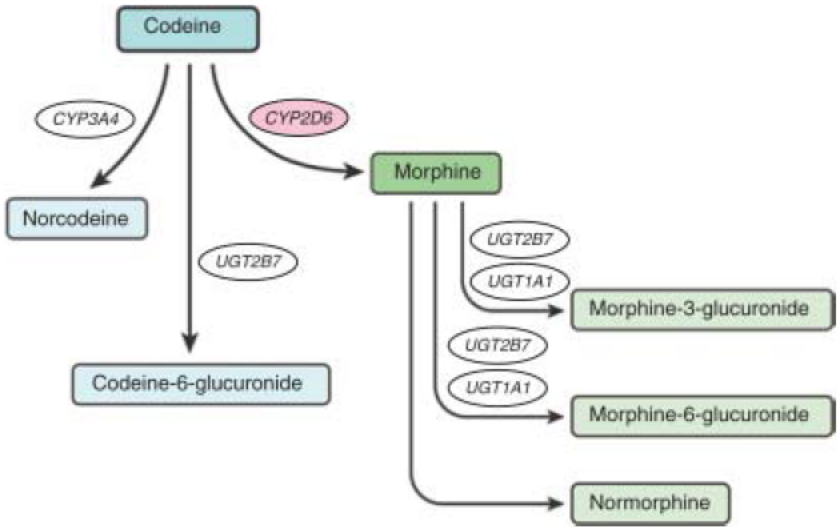
BACKGROUND

Codeine (as sulfate or phosphate in combination with acetaminophen) is an opioid analgesic related to morphine, indicated for the relief of mild to moderately severe pain. Codeine is widely prescribed for the management of post-tonsillectomy/adenoidectomy pain in children. FDA is aware of three deaths and two life-threatening cases of apnea in this population which have been documented in the medical literature since 2007. While some of these cases had mitigating factors, such as underlying bronchopneumonia, they share a consistent temporal relationship between codeine administration and death or life-threatening apnea. The purpose of this review is to summarize the clinical pharmacology and pharmacogenomics of codeine, and to provide a recommendation for the use of codeine in the pediatric population.

CODEINE PHARMACOGENETICS

The usual codeine dosage is 15 to 60 mg every 4 hours in adults and 0.5 mg/kg 3 to 4 times daily in children. For children, codeine is usually formulated with acetaminophen in liquids containing 12 mg of codeine and 120 mg of acetaminophen per 5 mL. The labeled dose is 10 mL 3 to 4 times daily in children 7 to 12 years of age, and 5 mL 3 to 4 times daily in children 3 to 6 years of age. Safe dosages in children under 3 years of age have not been established. Codeine sulfate alone is not indicated for pediatric use. Dosage should be adjusted according to severity of pain and response of the patient.

Codeine is an opioid analgesic related to morphine, but with less potent analgesic properties. Approximately 5-10% of codeine is converted to morphine by CYP2D6, which is in turn metabolized to the active moiety (M6-glucuronide) via UGT2B7, as shown in the figure below.



A high degree of variability exists for CYP2D6-mediated activation of codeine because of underlying genetic differences in CYP2D6 activity. Patients may be classified as having one of four metabolic phenotypes depending on the number of active genes the patient has, as shown in the table below.

Table 1. CYP2D6 genotype-derived phenotype frequency and definition

Predicted phenotype	Prevalence*	Genotypes	Examples of diplotypes
Ultrarapid metabolizer (UM)	~1–2%†	An individual carrying more than two copies of functional alleles	**1/*1xN, *1/*2xN*
Extensive metabolizer (EM)	~77–92%	An individual carrying two alleles encoding full or reduced function or one full function allele together with either one nonfunctional or one reduced-function allele	**1/*1, *1/*2, *2/*2, *1/*41, *1/*4, *2/*5, *10/*10*
Intermediate metabolizer (IM)	~2–11%	An individual carrying one reduced and one nonfunctional allele	**4/*10, *5/*41*
Poor metabolizer (PM)	~5–10%	An individual carrying no functional alleles	**4/*4, *4/*5, *5/*5, *4/*6*

* Frequency data are for Caucasians. Frequencies may differ substantially by race/ethnicity

† Ultrarapid metabolizer frequencies are as follows: African Americans, 3%; Arab, 16-28%; Caucasian, 1-10%; Chinese, 0.5-1%; Ethiopian, 16-28%; Hispanic, 0.5-1%; Japanese, 0.5-1%; North African, 16-28%

Patients with CYP2D6 dysfunction may have therapeutic failure secondary to reduced biotransformation of codeine to morphine. Conversely, UMs may be at risk of toxicity because of more rapid and complete conversion to morphine. For example, Sindrup, et al. evaluated oral codeine (75 mg) in 12 EMs and 12 PMs identified using urinary sparteine metabolic ratios to study plasma concentrations and therapeutic response.[1] The authors found that morphine was undetectable in PMs (< 4 nM) and peak morphine concentrations were between 4.9–37.6 nM in EMs. In the EM group, codeine significantly decreased the pain threshold caused by laser stimuli, whereas no significant analgesic effects were observed in the PM group. In a separate study, a single 50-mg dose of oral codeine dose led to a 20-fold higher AUC of morphine and M6-glucuronide in 8 EMs as compared to 6 PMs.[2] Individuals with the UM phenotype are at the highest risk for morphine exposure and toxicity, including respiratory depression. The codeine AUC and the C_{max} were not significantly different in UMs compared to EMs, although morphine AUC was 45.5% higher in UMs ($p<0.05$).[3] When examining outcomes, significantly more adverse effects were reported in the UM group compared with the EMs,[3] suggesting that risk for codeine toxicity is dependent on morphine exposure. The clinical and pharmacokinetic literature has been extensively reviewed by the Clinical Pharmacogenetics Implementation Consortium. Please see Crews, et al. Clin Pharmacol Ther 2012; 91: 321-6 for a detailed summary.

SAFETY OF CODEINE IN CHILDREN UNDERGOING TONSILLECTOMY AND/OR ADENOIDECTOMY

Tonsillectomy and adenoidectomy are among the most commonly performed operations in the pediatric population. Common indications for these procedures include obstructive sleep apnea syndrome (OSAS) or infection. In 2006, an estimated 530,000 tonsillectomies (with or without adenoidectomy) and 132,000 adenoidectomies (without tonsillectomy) were performed in patients < 15 years of age.[4] The majority of operations are performed as ambulatory, same-day procedures.[4]

Five cases of severe outcomes in children receiving codeine for pain management post-tonsillectomy/adenoidectomy have been reported in the published literature and are summarized below. All cases were between two and six years of age. In three cases, administration of codeine resulted in death; the other patients were hospitalized and required mechanical ventilation. Morphine concentrations were at the upper end of the usual distribution in these patients; two were identified as being UMs, while two others were EMs.

> *Case #1:* A 2-year-old boy weighing 13 kg with a history of snoring and sleep apnea underwent elective adenotonsillectomy. The outpatient surgery was uncomplicated and 6 hours after surgery the patient received 10 mg of meperidine and 12.5 mg of dimenhydrinate IM. The patient was sent home with instructions for 10 to 12.5 mg of codeine and 120 mg of acetaminophen syrup to be administered orally every 4 to 6 hours as needed for pain. The child developed fever and wheezing on the second evening after surgery. The next morning, the child was found dead. Postmortem examination revealed codeine and morphine concentrations of 0.7 mg/L (700 ng/mL) and 32 ng/mL, respectively. This reported codeine concentration far exceeds observed codeine Cmax value in adults after a single 60 mg oral dose (approximately 170 ng/mL), suggesting possible overdose. CYP450 genotyping demonstrated functional duplication of the

CYP2D6 allele resulting in the UM phenotype. Autopsy results also indicated evidence of bronchopneumonia, further enhancing the risk of hypoxemia.[5]

Case #2: A 4-year-old boy weighing 27.6 kg underwent adenotonsillectomy for OSAS with recurrent tonsillitis. The patient was discharged after an uneventful overnight stay on liquid codeine (8 mg per dose up to 5 times per day as needed for pain). The patient was reported to be sedated and lethargic on the day following the procedure. On the next day, the patient was found dead. The child received a total of 4 codeine doses for a total of 32 mg. Postmortem morphine serum concentrations were 17.6 ng/mL and genotyping revealed a gene duplication and a CYP2D6 UM phenotype (CYP2D6 *1/*2xN).[6]

Case #3: A 3-year-old girl weighing 14.4 kg underwent tonsillectomy for OSAS and was discharged after a 24-hour, uncomplicated hospital stay. The patient received two doses of codeine syrup (15 mg) while hospitalized. Upon discharge she prescribed codeine with acetaminophen (15 mg/150 mg) every 4 to 6 hours as needed for pain. The patient was given a total of 60 mg of codeine. Approximately 6 hours after her final codeine dose, the child was found unresponsive with fever. The patient was brought to the hospital with oxygen saturations of 65% where she received resuscitation, mechanical ventilation, and 1.5 mg of naloxone. Morphine concentrations were 17 ng/mL. The following day, the patient was extubated and recovered fully. Her genotype was determined to be an EM (CYP2D6 *1/*1).[6]

Case #4: A 5-year-old boy weighing 29 kg underwent adenotonsillectomy for recurrent tonsillitis. The patient was discharged on the day of surgery on acetaminophen with codeine (12 mg) every 4 hours. It appears that this prescription was scheduled (i.e. not as needed). The child was found without vital signs approximately 24 hours following the surgery. The postmortem morphine concentration was 30 ng/mL and the codeine concentration was 78 ng/mL. While this information is highly suggestive of CYP2D6 UM status, genotyping was not performed for this patient.[6]

Case #5: A 29-month-old male child weighing 13.7 kg underwent adenotonsillectomy for recurrent tonsillitis and OSAS. After the procedure, the patient received two doses of acetaminophen with codeine elixir at 1.5 mg/kg per dose during a 5 hour hospital stay. The child received four additional doses of acetaminophen with codeine on postoperative day 1. During the second night after surgery, the patient was found unresponsive and apneic. The child survived with 1.4 mg of naloxone along with ventilation control via intubation. Intensive care was provided for over a week. A urinary drug screen qualitatively confirmed the presence of opioids although morphine concentrations were not determined. Subsequent genotyping revealed a heterozygous variant, CYP2D6*1/*2 genotype, consistent with this individual being an extensive metabolizer.[7]

Table 1. Summary of codeine-related morbidity and mortality in pediatric patients post-tonsillectomy and/or adenoidectomy

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	2	4	3	5	2
Weight (kg)	13	27.6	14.4	29	13.7
Procedure	T/A	T/A	T	T/A	T/A
Outcome	Died	Died	Hospitalized, recovered	Died	Hospitalized, recovered
Dose based on 0.5 mg/kg	7.5 mg	14 mg	7.2 mg	14 mg	7 mg
Prescribed codeine dose	10 to 12.5 mg every 4 to 6 hours	8 mg up to five times daily	15 mg every 4 to 6 hours	12 mg every 4 hours	NR
Total amount of codeine administered	NR	32 mg	60 mg	NR	120 mg
Codeine concentration	700 ng/mL	NR	NR	78 ng/mL	NR
Morphine concentration	32 ng/mL	17.6 ng/mL	17 ng/mL	30 ng/mL	NR
Genotype*	NR	*1/*2xN	*1/*1	NR	*1/*2
Phenotype	UM	UM	EM	NR	EM
Reference	5	6	6	6	7

NR: not reported, T: tonsillectomy, A: adenoidectomy
* Genotyping methods are generally not described in sufficient detail in any of the case reports

.

Although these cases collectively represent a small fraction of the total pediatric adenotonsillectomy population, a recent report by Sadhasivam and Myer suggests the incidence of morbidity and mortality may be much greater.[8] In reviewing the LexisNexis database between 1984 and 2010 for death and injury claims following tonsillectomy, the authors conclude that 18% of death claims and 5% of injury claims (hypoxic brain injury) were secondary to opioids. Several opioids were associated with these claims, with codeine being the most frequently implicated. Finally, case reports also exist for children receiving codeine as an antitussive, suggesting that risks of codeine may not be limited to the adenotonsillectomy population.[9]

CLINICAL GUIDELINES FOR POST-TONSILLECTOMY/ADENOIDECTOMY PAIN MANAGEMENT

Clinical practice guidelines recommend postoperative pain control for children undgeroing tonsillectomy through the use of fluids, and scheduled use of ibuprofen and/or other pain medications, but do not recommend specific analgesics. With regard to codeine, the guidelines acknowledge that codeine may be ineffective or toxic because of genetic variations in CYP2D6, and evidence does not support superiority over acetaminophen alone. However, acetaminophen

alone may be inadequate. The guidelines also acknowledge bleeding risks associated with the platelet inhibiting effects of nonsteroidal anti-inflammatory drugs but express limited concern about their use except for ketorolac.

ALTERNATIVES TO CODEINE

Acetaminophen alone: The effectiveness of codeine for pain management post-adenotonsillectomy has been compared to alternative analgesics. A study appearing in *Laryngoscope* in 2000 investigated acetaminophen versus acetaminophen plus codeine in a prospective, randomized, double-blind fashion.[10] The results show that in 51 children aged 3 to 12 years there was no difference ($p > 0.05$, all time points) in postoperative pain control when codeine was prescribed along with acetaminophen. Additionally, the acetaminophen with codeine group tended to have increased nausea and emesis, though the differences did not reach statistical significance. A different study found that acetaminophen plus honey was more effective than acetaminophen alone for post-tonsillectomy/adenoidectomy pain control in children.[11]

Acetaminophen with other opioids: Acetaminophen with hydrocodone may also be effective in controlling pain in children undergoing outpatient tonsillectomy.[12] However, hydrocodone is metabolized in a CYP2D6-dependent manner to more potent hydromorphone[13], again raising the possibility of opioid-related adverse effects in UMs. A study in adults showed that oxycodone significantly reduced postoperative pain after tonsillectomy[14], though pediatric data is not available and oxycodone is not indicated for patients < 18 years of age. Oxycodone is metabolized to noroxycodone by CYP3A4, noroxymorphone by both CYP2D6 and CYP3A4, and oxymorphone by CYP2D6. The analgesic effect is primarily due to the parent compound.

NSAIDs: Other available data in pediatrics suggests that ibuprofen provides more effective analgesia than codeine for alternative indications, such as musculoskeletal trauma. In a study of 300 children, ibuprofen provided superior pain control to acetaminophen and codeine for the treatment of acute traumatic musculoskeletal injuries.[15] Ibuprofen has also been evaluated against acetaminophen with codeine for post-tonsillectomy pain. [16] The results show that acetaminophen with codeine was more effective in controlling pain on days 1 and 3 ($p = 0.04$ and 0.03, respectively) but no difference was seen between the treatment groups ($p = 0.2$) by day 5. However, the postoperative bleeding rate was 0% in the acetaminophen-with-codeine group and 12.5% in the ibuprofen group. Thus, concerns over bleeding risk may limit NSAID use in children. Nonetheless, discrepant evidence exists regarding bleeding. In a separate larger retrospective study (n=1160), ibuprofen was not associated with postoperative bleeding in pediatric patients following adenotonsillectomy.[17] A review from the Cochrane Collaboration based on data from 13 randomized controlled trials found that NSAIDs did not increase bleeding risk compared with placebo or other analgesics (odds ratio, 1.46; 95% CI, 0.49-4.40). Excluding trials of ketorolac (leaving 7 trials involving 567 children), the risk for bleeding requiring reoperation was not increased by NSAIDs, (odds ratio, 0.91 95% CI, 0.22-3.71).[18] The COX-2 inhibitor celecoxib, which is associated with less bleeding than NSAIDs, has also been evaluated for pain management following tonsillectomy.[19] The results demonstrate that celecoxib is associated with earlier cessation of pain during eating and less postoperative bleeding as

compared to ketoprofen. However, no head-to-head comparison between COX-2 inhibitors and opioids has been performed.

Overall, the available evidence strongly suggests that codeine is no more effective than either acetaminophen or acetaminophen with honey. The acetaminophen-containing regimens may carry a more favorable safety profile in light of the recent instances of death and life-threatening apnea with codeine. Ibuprofen is also a viable option, although prescribers may avoid its use due to bleeding concerns.

CLINICAL UTILITY OF CYP2D6 GENOTYPING

FDA has cleared several assays for the diagnostic analysis of CYP2D6 genes (e.g., AmpliChip [Roche], xTAG [Luminex]) and other tests are available to prescribers (e.g., through LabCorp or Quest Diagnostics). In the setting of codeine use, such tests could allow for identification of patients with the UM phenotype for whom codeine may carry increased risk. Reported cases of death and morbidity related to codeine are rare based on drug utilization estimates in children (see review by Office of Surveillance and Epidemiology). Given that the prevalence of UM is rather high in some populations, many UMs presumably receive codeine without incident. Consequently, the positive predictive value for adverse outcomes is likely to be low, and the consequent number needed to screen to prevent a single event is likely to be exceedingly high. Genotyping also appears imprecise given that some cases were EMs and not UMs. Finally, preoperative laboratory data are not routinely obtained for tonsillectomy, and it is unclear if genotyping could be routinely implemented.

LABELING OF CODEINE PRODUCTS RELATED TO CYP2D6 ULTRARAPID METABOLISM

The labeling for codeine sulfate and phosphate products currently contain information about UMs as shown below:

> WARNINGS AND PRECAUTIONS
> …
> 5.9 Ultra-Rapid Metabolizers of Codeine
> Some individuals may be ultra-rapid metabolizers due to a specific CYP2D6*2x2 genotype. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing.
>
> The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups.
>
> When physicians prescribe codeine-containing drugs, they should choose the lowest effective dose for the shortest period of time and inform their patients about these risks and the signs of morphine overdose. [see 8 USE IN SPECIFIC POPULATIONS]
>
> USE IN SPECIFIC POPULATIONS
> …

8.3 Nursing Mothers

Codeine is secreted into human milk. In women with normal codeine metabolism (normal CYP2D6 activity), the amount of codeine secreted into human milk is low and dose-dependent. However, some women are ultra-rapid metabolizers of codeine. These women achieve higher-than-expected serum levels of codeine's active metabolite, morphine, leading to higher-than-expected levels of morphine in breast milk and potentially dangerously high serum morphine levels in their breastfed infants. Therefore, maternal use of codeine can potentially lead to serious adverse reactions, including death, in nursing infants.

The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups.

The risk of infant exposure to codeine and morphine through breast milk should be weighed against the benefits of breastfeeding for both the mother and the baby. Caution should be exercised when codeine is administered to a nursing woman. If a codeine containing product is selected, the lowest dose should be prescribed for the shortest period of time to achieve the desired clinical effect. Mothers using codeine should be informed about when to seek immediate medical care and how to identify the signs and symptoms of neonatal toxicity, such as drowsiness or sedation, difficulty breastfeeding, breathing difficulties, and decreased tone, in their baby. Nursing mothers who are ultra-rapid metabolizers may also experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing. Prescribers should closely monitor mother-infant pairs and notify treating pediatricians about the use of codeine during breastfeeding. [see 5 WARNINGS AND PRECAUTIONS]

SUMMARY OF CLINICAL PHARACOLOGY FINDINGS

- Death and hospitalization related to codeine toxicity following tonsillectomy/adenoidectomy have been reported in children who are CYP2D6 extensive and ultrarapid metabolizers or who had evidence of high exposures to morphine.

- CYP2D6 produces an active metabolite of codeine. A significant portion of patients are likely to either derive no therapeutic benefit from codeine (i.e. CYP2D6 poor metabolizers) or be at risk for morphine toxicity (i.e. CYP2D6 extensive or ultrarapid metabolizers). Much of the existing labeling covers the role of CYP2D6 phenotype in codeine metabolism.

- While genotyping could offer an advantage to identify at-risk patients, practical considerations limit its application, including low predictive value, high numbers needed to screen, and limited preoperative laboratory assessments.

- The reports of codeine toxicity appear to be limited to children with a history of sleep apnea who undergo tonsillectomy and/or adenoidectomy, although case reports exist for children receiving codeine as an antitussive.[9] Thus, it would be reasonable to extend any warnings or dosing recommendations (i.e., lowest dose as needed) beyond pain indications.

- Drug and non-drug alternatives to codeine are available. Acetaminophen alone or with honey, may be as effective as acetaminophen with codeine for post-adenotonsillectomy pain management. Ibuprofen is also effective, though it has been associated with bleeding. For persistent or severe pain, administering morphine would be preferred over codeine (bypassing variable codeine metabolism), but carries theoretical risks for overdose resulting from administration errors.

– Current practice guidelines put forth by the American Academy of Otolaryngology (AAO)[20] recommend that ibuprofen may be used for pain control after surgery and notes that codeine offers no benefit over acetaminophen. Members of the American Academy of Pediatrics Committee on Drugs advocate for the use of products with less phenotypic variability (e.g. morphine, oxycodone, hydrocodone) in lieu of codeine.

RECOMMENDATION

The labeling for codeine products should be revised to advise prescribers about the risk for severe outcomes in children who receive codeine for pain management following tonsillectomy and/or adenoidectomy, and that use of codeine should be avoided in this patient population, regardless of genotype. If codeine must be used in children, regardless of the indication, labeling should indicate that it be administered at the lowest approved dose for the shortest duration on an as-needed basis.

REFERENCES

1. Sindrup SH, Brosen K, Bjerring P, et al. Codeine increases pain thresholds to copper vapor laser stimuli in extensive but not poor metabolizers of sparteine. *Clinical pharmacology and therapeutics.* Dec 1990;48(6):686-693.

2. Yue QY, Hasselstrom J, Svensson JO, Sawe J. Pharmacokinetics of codeine and its metabolites in Caucasian healthy volunteers: comparisons between extensive and poor hydroxylators of debrisoquine. *British journal of clinical pharmacology.* Jun 1991;31(6):635-642.

3. Kirchheiner J, Schmidt H, Tzvetkov M, et al. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. *The pharmacogenomics journal.* Aug 2007;7(4):257-265.

4. Cullen KA, Hall MJ, Golosinskiy A. Ambulatory surgery in the United States, 2006. *National health statistics reports.* Jan 28 2009(11):1-25.

5. Ciszkowski C, Madadi P, Phillips MS, Lauwers AE, Koren G. Codeine, ultrarapid-metabolism genotype, and postoperative death. *The New England journal of medicine.* Aug 20 2009;361(8):827-828.

6. Kelly LE, Rieder M, van den Anker J, et al. More codeine fatalities after tonsillectomy in North American children. *Pediatrics.* May 2012;129(5):e1343-1347.

7. Voronov P, Przybylo HJ, Jagannathan N. Apnea in a child after oral codeine: a genetic variant - an ultra-rapid metabolizer. *Paediatric anaesthesia.* Jul 2007;17(7):684-687.

8. Sadhasivam S, Myer Iii CM. Preventing opioid-related deaths in children undergoing surgery. *Pain medicine.* Jul 2012;13(7):982-983.

9. Hermanns-Clausen M, Weinmann W, Auwarter V, et al. Drug dosing error with drops: severe clinical course of codeine intoxication in twins. *European journal of pediatrics.* Jul 2009;168(7):819-824.

10. Moir MS, Bair E, Shinnick P, Messner A. Acetaminophen versus acetaminophen with codeine after pediatric tonsillectomy. *The Laryngoscope.* Nov 2000;110(11):1824-1827.

11. Ozlugedik S, Genc S, Unal A, Elhan AH, Tezer M, Titiz A. Can postoperative pains following tonsillectomy be relieved by honey? A prospective, randomized, placebo

controlled preliminary study. *International journal of pediatric otorhinolaryngology.* Nov 2006;70(11):1929-1934.

12. Sutters KA, Miaskowski C, Holdridge-Zeuner D, et al. A randomized clinical trial of the efficacy of scheduled dosing of acetaminophen and hydrocodone for the management of postoperative pain in children after tonsillectomy. *The Clinical journal of pain.* Feb 2010;26(2):95-103.

13. Smith HS. The metabolism of opioid agents and the clinical impact of their active metabolites. *The Clinical journal of pain.* Nov-Dec 2011;27(9):824-838.

14. Vaiman M, Krakovski D, Haitov Z. Oxycodone and dexamethasone for pain management after tonsillectomy: a placebo-controlled EMG assessed clinical trial. *Medical science monitor : international medical journal of experimental and clinical research.* Oct 2011;17(10):PI25-31.

15. Clark E, Plint AC, Correll R, Gaboury I, Passi B. A randomized, controlled trial of acetaminophen, ibuprofen, and codeine for acute pain relief in children with musculoskeletal trauma. *Pediatrics.* Mar 2007;119(3):460-467.

16. Harley EH, Dattolo RA. Ibuprofen for tonsillectomy pain in children: efficacy and complications. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Nov 1998;119(5):492-496.

17. Jeyakumar A, Brickman TM, Williamson ME, et al. Nonsteroidal anti-inflammatory drugs and postoperative bleeding following adenotonsillectomy in pediatric patients. *Archives of otolaryngology--head & neck surgery.* Jan 2008;134(1):24-27.

18. Cardwell M, Siviter G, Smith A. Non-steroidal anti-inflammatory drugs and perioperative bleeding in paediatric tonsillectomy. *Cochrane database of systematic reviews.* 2005(2):CD003591.

19. Nikanne E, Kokki H, Salo J, Linna TJ. Celecoxib and ketoprofen for pain management during tonsillectomy: a placebo-controlled clinical trial. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Feb 2005;132(2):287-294.

20. Baugh RF, Archer SM, Mitchell RB, et al. Clinical practice guideline: tonsillectomy in children. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Jan 2011;144(1 Suppl):S1-30.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MICHAEL A PACANOWSKI
10/05/2012

GILBERT J BURCKART
10/05/2012

YUN XU
10/05/2012

OFFICE OF CLINICAL PHARMACOLOGY

CLINICAL PHARMACOLOGY REVIEW

Drug Name	Codeine
Application	Safety TSI 1319 dated 4/12/12
Primary Reviewers	Sheetal Agarwal, Ph.D., RAC and Christian Grimstein Ph.D.
Supervisors	Chandra Sahajwalla, Ph.D., and Mike Pacanowski, Pharm.D., MPH
OCP Divisions	Division of Clinical Pharmacology 2, Immediate Office
OND Divisions	ODEII/DPARP, ODEII/DAAAP
Indication(s)	Use of codeine in children (18 years and under) for cough/cold and relief of mild to moderately severe pain

BACKGROUND

In April 2015, the European Medicines Agency (EMA) completed a review of the use of codeine for cough and cold indications and contraindicated the use of codeine in children below 12 years of age for cough and cold and recommended that codeine not be used in children and adolescents between 12 and 18 years who have breathing problems. In lieu of this decision made by the EMA, the FDA decided to review and discuss the use of codeine products for cough and cold indications in the US in children below 18 years of age. An Advisory Committee (AC) meeting is scheduled for December 10, 2015, to discuss the safety of codeine for the relief of cough and symptoms associated with upper respiratory allergies or common cold in pediatric patients and whether contraindication in pediatric patients is warranted. More background information can be found in the background document written for the AC. This OCP short review is an addendum to a previously written detailed review authored by Dr. Jeremiah Momper (dated 10/05/2012 and attached at the end of this review) which summarized pharmacogenetics (PGx) of codeine and described 5 case reports related to use of codeine in patients for pain relief after tonsillectomy and/or adenoidectomy. This review will focus on the use of codeine in cough/cold indications. In addition, OCP was tasked with reviewing the 64 adverse event case reports (FAERS database) identified by the office of surveillance and epidemiology (OSE) reviewers in relation to the use of codeine in children. In this short addendum, we will summarize PGx findings as well as information related to codeine/morphine drug levels included in the case reports.

OVERALL CONCLUSION

From our review of the FAERS reports, we conclude that (a) codeine toxicity at therapeutic doses of codeine may occur in children who are CYP2D6 extensive and ultra-rapid metabolizers

and (b) codeine toxicity may occur in children taking higher than recommended therapeutic doses (overdosing or concomitant administration of multiple opioid drug products).

CODEINE DOSING IN COUGH/COLD INDICATIONS

Codeine is indicated for the relief of cough and is available in combination with other medications in prescription products for cough and symptoms associated with upper respiratory allergies or the common cold. The table below (borrowed from the background package document) includes the available prescription codeine products in children below 18 years, for cough/cold indications, including the dosing information and the relevant pediatric labeling.

Codeine dose in children for codeine combined with promethazine (with or without phenylephrine) is:

a. 12 years and up: 10 mg every 4 to 6 hours not to exceed 60 mg in 24 hours
b. 6-12 years: 5-10 mg every 4 to 6 hours not to exceed 60 mg in 24 hours

Codeine dose in children for codeine combined with pseudoephedrine and triprolidine:

a. 12 years and up: 20 mg every 4 to 6 hours not to exceed 80 mg in 24 hours
b. 6-12 years: 10 mg every 4 to 6 hours not to exceed 40 mg in 24 hours
c. 2-6 years: 5 mg every 4 to 6 hours not to exceed 20 mg in 24 hours

Available Prescription Codeine Products for Cough/Cold Indication

Application	Product	Dosage Form and Dose	Relevant Pediatric Labeling
NDA 8306 ANDA (multiple)	codeine phosphate 10 mg/5 mL; phenylephrine hydrochloride 5 mg/5 mL; promethazine hydrochloride 6.25 mg/5 mL	Oral Syrup	Contraindication in children < 6 yrs; Boxed Warning regarding respiratory depression in children (promethazine/codeine combo) Boxed Warning regarding deaths related to ultra-rapid metabolism of codeine to morphine Contraindication for postoperative pain management in children post T&A **Dosing information in children:** **Dosing in children 12 years and up: 1 teaspoonful (5 mL) every 4 to 6 hours, not to exceed 30 mL in 24 hours.** **Dosing in children 6-12 years: ½ to 1 teaspoonful (2.5 to 5 mL) every 4 to 6 hours, not to exceed 30 mL in 24 hours.**
NDA 8306 ANDA (multiple)	codeine phosphate 10 mg/5 mL; promethazine hydrochloride 6.25 mg/5 mL	Oral Syrup	

ANDA 88704 (Sti Pharma)	codeine phosphate 10 mg/5 mL; pseudoephedrine hydrochloride 30 mg/5 mL; triprolidine hydrochloride 1.25 mg/5 mL (Triacin C)	Oral Syrup	Boxed Warning regarding deaths related to ultra-rapid metabolism of codeine to morphine Contraindication for postoperative pain management in children post T&A **Dosing information in children:** **Dosing in children 12 years and up: 2 teaspoonfuls (10 mL) every 4 to 6 hours, not to exceed 8 teaspoonfuls (40 mL) in 24 hours.** **Dosing in children 6-12 years: 1 teaspoonful (5 mL) every 4 to 6 hours, not to exceed 4 teaspoonfuls (20 mL) in 24 hours.** **Dosing in children 2-6 years: ½ teaspoonful (2.5 mL) every 4 to 6 hours, not to exceed 2 teaspoonfuls (10 mL) in 24 hours.**
Source: FDA Orange Book search on June 4, 2015 and DailyMed for labeling content on October 5, 2015			

CODEINE METABOLISM AND ACTIVE METABOLITES

About 70-80% of the administered dose of codeine is metabolized by conjugation with glucuronic acid to codeine-6-glucuronide (C6G, about 60%) and via *O*-demethylation to morphine (about 5-10%) and *N*-demethylation to norcodeine (about 10%) respectively. UDP-glucuronosyltransferase (UGT) 2B7 and 2B4 are the major enzymes mediating glucurodination of codeine to C6G. Cytochrome P450 2D6 is the major enzyme responsible for conversion of codeine to morphine (about 5-10%) and P450 3A4 is the major enzyme mediating conversion of codeine to norcodeine. Morphine and norcodeine are further metabolized by conjugation with glucuronic acid. The glucuronide metabolites of morphine are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). (Source: Approved label for codeine sulfate oral solution NDA 202245)

Pharmacological activity of codeine and its metabolites in pain:

Codeine is an opioid agonist, related to morphine, but with less potent analgesic properties. The analgesic properties of codeine have been speculated to come from its conversion to morphine, although the exact mechanism of analgesic action remains unknown. Morphine and M6G are known to have analgesic activity in humans. The analgesic activity of C6G in humans is unknown. Norcodeine and M3G are generally not considered to possess analgesic properties. (Source: Approved label for codeine sulfate oral solution NDA 202245)

Pharmacological activity of codeine in cough/cold:

Codeine is historically believed to possess anti-tussive properties. Codeine's anti-tussive use is recognized in a monograph (21cfr341.74) and codeine containing products at doses included in the monograph can be marketed over the counter for cough indications. From literature, this reviewer did not find any articles indicating that morphine or any other codeine metabolites have anti-tussive properties.

CYP2D6 MATURATION AND FUNCTIONAL ACTIVITY

A published article titled 'Developmental Changes in Human Liver CYP2D6 Expression' (Drug Metab Dispos. 2008 Aug; 36(8):1587-93) reported that there were no significant differences in either CYP2D6 protein or activity with increasing age after 1 week postnatal age (up to the age of 18 years).

SUMMARY OF FINDINGS FROM AERS REPORTS

For the AC meeting to be held on 12/10/2015, OSE was consulted to provide a summary of any case reports associated with use of codeine in pediatric patients. OSE reviewer Annie Nguyen provided a total of 64 case reports from the FAERS data base that reported use of codeine in pediatric patients, irrespective of the indication (cough/cold and analgesia among other indications are included).

Table 1 includes a summary of the type of clinical pharmacology information that was available in the 64 FAERS case reports.

Table 2 includes a summary of the cases (N=8) which reported a confirmed or suspected PGx component that were not included in the previous clinical pharmacology review, dated 10/5/2012. Death and hospitalization were reported in children 3-13 years of age who were treated for pain or cough. With only limited data available regarding CYP2D6 genotype/phenotype and blood codeine/morphine levels, the cases confirm previous reports that codeine toxicity occurs in CYP2D6 extensive and ultra-rapid metabolizers and patients with evidence of high exposures to morphine. A description of the 8 cases is also included following Table 2.

Table 3 includes a summary of the N=7 cases in which blood level information for codeine and/or morphine was reported (no PGx information was available in these 7 case reports). In all 7 cases, the outcome was death and all reported increased blood levels of codeine and/or morphine suggesting increased opiate exposures contributed to outcome. A published article titled 'Postmortem redistribution of morphine and its metabolites' indicates that 'significant postmortem redistribution of morphine and its metabolites seems unlikely.' As such the reported blood levels of morphine may be representative of the systemic concentrations in the subjects at the time of their death. Five of the 7 case reports indicate codeine/morphine

overdosing due to overdosing of the opioid product or multiple opioid products being co-administered, one report indicates respiratory depression due to sedation by both opioid and diazepam being taken concomitantly and one report indicates the child was taking the opioid with divalproex, which is not indicated to interfere with opioid metabolism, so it is possible that this child was overdosed with the opioid product in a short amount of time.

Table 1: Summary of clinical pharmacology information included in N=64 FAERS case reports

Total reports	**N=64**
PGx information included	N=13
PGx role confirmed based on the report	N=9 FAERS # 6365935 (same as 7723833), 6876687, 8418987 (same as 8522044), 8418989 (same as 8676907), 8522228 (same as 9443899), 9856393, 7371901, 8760324 and 9165725
PGx role suspected by the medical staff or the reporter	N=4 FAERS # 6959752, 6959806, 9856399 and 9397006
PGx cases that were covered in previous clinical pharmacology review and not described in this review	N=5 FAERS # 6365935 (same as 7723833), 8418987 (same as 8522044), 8418989 (same as 8676907), 8522228 (same as 9443899) and 6876687
Blood levels of codeine and/or morphine included **(Case reports that included levels of drugs other than codeine and/or morphine were not included in our review)**	N=11 FAERS # 6516302, 6876687 (PGx role confirmed), 6959752 (PGx role confirmed), 6959806 (PGx role confirmed), 4293693, 5788170, 6454487, 8522228 (PGx role suspected), 9382047, 8749396, 9379348

Table 2: Summary of codeine-related morbidity and mortality in pediatric patients

FAERS Case #/ report date	**6959752/ Apr-3-2009**	**6959806/ Apr-3-2009**	**9856399/ Jan-30-2014**	**9397006/ Jul-9-2013**	**7371901/ Apr-21-2010**	**8760324/ Aug-28-2012**	**9165725/Mar-4-2013**	**9856393/ Jan-30-2014**
Age (years)	3	3	3	13	3	4	8	12
Weight (kg)	14	13	NR	73	15	13	40	NR
Indication	Cough	Cough	Pain	Pain	Pain	Pain	Pain	Pain
Outcome	Death	Hospitalized, recovered	Death	Recovered	Hospitalized/Recovered	Hospitalized/ Recovered	Hospitalized /Recovered	Death
Dose based on 0.5mg/kg	7 mg	6.5 mg	NR	37 mg	7.5 mg	6.5 mg	20	NR
Prescribed codeine dose	0.5 mL (10mg) qd	0.5 mL (10mg) qd	NR	30mg q6h	5-7.5 mL q4-6h	5mL (12mg) q6h	NR	NR
Total amount of codeine administered	75 mg	75 mg	NR	30mg	NR	36mg	NR	NR

Codeine (total) concentration	645 ng/mL	489 ng/mL	NR	NR	NR	NR	NR	NR
Morphine (total) concentration	426 ng/mL	312 ng/mL	NR	NR	NR	NR	NR	High (unspecified) levels reported
Genotype	NR	NR	NR	*1/*2x3	NR	NR	NR	NR
Phenotype	EM	EM	UM	UM	UM suspected by the reporter	UM suspected by the reporter	UM suspected by the reporter	UM suspected by the reporter

NR: Not reported; EM: Extensive metabolizer; UM: Ultra-rapid metabolizer

Description of cases: 4 confirmed cases: 2 in cough, 2 in pain patients

- FAERS Case #s 6959752, and # 6959806, Foreign, Death and Hospitalization, 2012: A literature report[1] of two 3-year-old monozygotic twins with history of upper respiratory tract infection for several days. The twins received codeine once daily over 6 days for cough with fever. The mother had applied 10 drops (=12.5mg) instead of the recommended 0.5ml (=10mg of codeine) daily. Twin 1 (13kg) was found apneic and lying in vomit by his mother at night. On admission to the hospital, the child was in coma (GCS 3) and had to be ventilated but eventually recovered. Twin 2 (14kg) was found dead in his bed by his father two and a half hours after the mother had called emergency services because of twin 1. The child was lying in vomit. Post mortem examination revealed massive aspiration of gastric contents and diffuse cerebral edema. Twin 1 serum codeine (total) concentration was 489ng/ml, and morphine (total) concentration was 312ng/ml, 7.5 h after last dosing. Deceased twin 2 serum codeine (total) concentration was 645ng/ml, and morphine (total) concentration was 426 ng/ml, blood was collected 7h after death. The twins had identical CYP2D6 gene polymorphisms and were extensive metabolizers.
- FAERS Case # 9856399, US, Death, 2014: Reported by physician. A 3-year-old child (sex unknown) had undergone tonsillectomy and had received codeine for postoperative pain. On postoperative day 3, the child was found dead. Postmortem genetic testing revealed the child was a CYP2D6 ultra-rapid metabolizer. Serum codeine and/or morphine levels were not reported.
- FAERS Case # 9397006, US, hospitalization, 2013: Reported by physician. After receiving one dose acetaminophen with codeine (30mg) for pain, a 13-year old female of African-American descent with history of Sickle-Cell disease, was unable to appropriately respond to questions, became very difficult to arouse and slept for most of the day.

[1] Hermanns-Clausen M, Weinmann W, Auwaerter V, et al. Drug dosing error with drops – severe clinical course of codeine intoxication in twins. Eur J Pediatr (2009) 168:819-824

Patient had previous prescriptions over lifetime. Mother did not call MD or pharmacy, because she considered the drowsiness as a normal side effect of the drug. The patient underwent genetic testing for CYP2D6 and was found to be a CYP2D6 ultra-rapid metabolizer (*1/*2-3N). Serum codeine and/or morphine levels were not reported.

Description of cases: 4 suspected cases: all in pain patients

- FAERS case # 7371901 (reported by parent on 04/21/2010): A 2.5-year-old boy weighing 34 lb underwent adenoidectomy and tonsillectomy to treat sleep apnea (day 1). The patient was discharged the next day of surgery (day 2) on Tylenol (acetaminophen) with codeine syrup to be given every 4-6 hours. On day 4, the patient is reported being wheezy and breathing fast and the parent gave the child albuterol. On day 5, the child awoke with fever and labored breathing, and was taken to see his pediatrician who recommended stopping the Tylenol with codeine and prescribed Motrin and antibiotics instead. On day 7, the child cried and complained of stomach hurt, passed out within 5-7 mins and became unconscious. The parent called 911 and the child was taken to the ER. In the ER many tests including bloodwork was performed but no explanation for the incident. The child is said to have recovered. The parent writes that they read about a case of ultra-rapid metabolism in published articles and thinks this is what happened to the child and would like for him to be tested for that in the future.
- FAERS case # 8760324 (reported by mother on 08/28/2012): A 4-year-old boy (28 lb) underwent let sided orchiopexy and inguinal hernia exploration on day 1. Was given 3 doses of Tylenol (acetaminophen) with codeine syrup (5 mL each time) per the reporter and developed respiratory failure on day 2. The mother indicates that he had Tylenol in 2009 when he underwent surgery for obstructive sleep apnea and had done well at that time. She reports that it was suspected that her son is an ultra-rapid metabolizer of codeine. The report is classified as an adverse event indicating the boy eventually recovered.
- FAERS case # 9165725 (reported by mother on 03/04/2013): An 8-yr old girl (88 lb) underwent adenotonsillectomy (AT), sinus surgery and nasal reconstruction. Post-surgery, she was medicated with Tylenol with codeine every 4 hours. She began having respiratory problems soon after her first dose and problems continued for 18 hours until she was in a respiratory arrest. She was given 2 doses of Narcan (naloxone) with good initial effect after first dose. Her lungs are reported to have been collapsed on both sides and is said to be somnolent and overdosed. She was thought to have encephalitis and had an MRI, she was in ICU for 18 hours and in hospital for 6 days. The mother indicates that tylenol with codeine rapidly metabolized in her liver converting to morphine and overdosing their daughter. The mother indicates that blood work was conducted but levels are not reported.

- FAERS case # 9856393 (reported by physician on 01/30/2014): A 12 yr-old child (M/F unknown) had undergone tonsillectomy and had received codeine for postoperative pain. The child was found unresponsive on postoperative day 2 (outcome: death). The report indicates that at autopsy, blood levels of morphine were found to be high, and indicates that patient could have been a rapid metabolizer.

Table 3: Codeine/Morphine blood levels reported in children

FAERS case # and recd. date	Demographic info.	Codeine dose and indication info.	Concomitant meds. info	Blood and urine drug level info.	Outcome and additional info.
6516302 11/29/2010	2 yr-old M	Codeine Phosphate every 4 hours for aphthous stomatitis: took a total of 3 doses every 4 hours	DIVALPROEX SODIUM	Codeine (total) 3153 mg/L and morphine (total) 1889 mg/L	Sudden death. Report says high levels of both codeine and morphine in blood and lethal level of codeine.
4293693 03/27/1975	3 month F	ACTIFED C syrup (triprolidine, PSE and codeine) ½ teaspoon TID for fever and cold: given twice the recommended dose by the mother (1 teaspoon QID)	V-CILLIN	Codeine 12 mcg/mL	Death. Day 1: recommended dosing, day 3: **overdosing**, day 5: unresponsive, day 9: death in hospital.
5788170 04/21/2005	9 yr-old M	Capital with codeine (APAP and codeine) oral suspension for sore throat after surgery (120mg/12 mg per 5 mL), given 15 mL supposedly post-surgery		Codeine 344 ng/mL and morphine 50 ng/mL	Death (asphyxia due to **opiate overdose**). Report says blood hydrocodone was 31ng/mL (therapeutic level is 20), codeine 344 (therapeutic level of30-120) and morphine 50 within therapeutic level of 30-100
6454487 10/19/2007	11 yr-old M (45 kg)	Unknown which form of codeine	BENADRYL MORPHINE OXAZEPAM DIAZEPAM ATROPINE PHENERGAN (PROMETHAZINE)	Codeine 0.03 mcg/mL and morphine 7.11 mcg/mL (blood) and 7000 ng/mL (urine)	Death (**morphine overdose**). Report says therapeutic level of codeine and lethal level of morphine in blood and urine. Many other drugs (not opiates) were also found in the blood.
9382047	10 yr-old F	APAP and codeine	DIAZEPAM (2-4	Codeine (total)	Death (Codeine

07/03/2013	(45 kg con sidered overweigh t)	oral suspension for pain (120mg/12 mg per 5 mL), 20 to 40 mg codeine every 4 hours as needed for pain post orthopedic surgery (two doses total) corresponding to 0.45-0.9 mg/kg PO	mg PO every 4 hours as needed (one dose)) BUDESONIDE MULTIVITAMIN	0.78 mg/L and morphine (not mentioned if free or total) 0.15 mg/L	toxicity, Pulmonary edema, Respiratory depression). Report says levels were in toxic range and **combined sedative effects of the opioid and benzodiazepine most likely caused respiratory depression**.
8749396 08/08/2012	14 yr-old M (250 lb)	APAP and codeine oral suspension for pain (120mg/12 mg per 5 mL) in ER for pain related to abscess	**KADIAN (MORPHINE ER)** CAPS 200 MG CLONIDINE TABS 0.3 MG SERTRALINE TABS 100 MG QUETIAPINE VALPROIC ACID LISDEXAMPHET AMINE DIPHENHYDRA MINE PENICILLIN MELOXICAM ARIPIPRAZONE	Codeine 117 ng/mL in blood and more than 10,000 ng/mL in urine and morphine 11.8 ng/mL in blood and 5069 ng/mL in urine	Death. Many other drugs (not opiates) were also found in the blood.
9379348 06/25/2013	6 yr-old F (45 kg)	CHERATUSSIN AC (guaifenesin and codeine oral solution 100 mg/10 mg per 5 mL) at a dose of 0.22-0.44 mg/kg every 4 hours (took a total of 3 doses) for respiratory infection with cough. Rx labeling error 1-2 teaspoonfuls every 4 h instead of prescribed dose.		Codeine (total) 0.17 mg/mL and morphine (total) 0.08 mg/mL	Death: **higher dose of codeine due to Rx labeling error**. Report says levels are within toxic range for an opioid naïve child.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHEETAL S AGARWAL
10/28/2015

CHRISTIAN GRIMSTEIN
10/28/2015

MICHAEL A PACANOWSKI
10/28/2015

CHANDRAHAS G SAHAJWALLA
10/29/2015

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Post-marketing Epidemiological, Pharmacovigilance, and Drug Utilization Review

Date:	11/13/2015
Reviewers:	Tracy Pham, Pharm.D. Drug Utilization Data Analyst, Division of Epidemiology II (DEPI-II) Annie Nguyen, R.Ph. Safety Evaluator, Division of Pharmacovigilance I (DPV-I) Catherine Dormitzer, Ph.D., MPH Epidemiologist, DEPI-II
Team Leaders:	Rajdeep Gill, Pharm.D. Drug Utilization Data Team Leader, DEPI-II Eileen Wu, Pharm.D. Safety Evaluator Team Leader, DPV-I Margie Goulding, Ph.D. Epidemiology Team Leader, DEPI-II
Deputy Directors:	Grace Chai, Pharm.D. Deputy Director for Drug Utilization, DEPI-II David Moeny, R.Ph., MPH, DEPI-II
Division Director:	Robert Levin, M.D., DPV-I
Subject:	Drug utilization and safety review of cough/cold and analgesic codeine-containing products in pediatric population (0-18 years) as background for the 12/10/15 joint PADAC-DSaRM AC meeting
Drug Name(s):	Cough/Cold and Analgesic Codeine-Containing Products
Application Type/Number:	Multiple
Applicant/Sponsor:	Multiple
OSE RCM #:	2015-1124

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information have been cleared to be released to the public/non-FDA personnel with contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

TABLE OF CONTENTS

EXECUTIVE SUMMARY

At the request of the Division of Pulmonary, Allergy and Rheumatology Products in the Office of New Drugs, the Division of Pharmacovigilance I (DPV-I) and Division of Epidemiology II (DEPI-II) in the Office of Surveillance and Epidemiology (OSE) undertook reviews to assess the safety and utilization of codeine-containing products in children. This review is provided as background information for a joint Pulmonary Allergy Drug Advisory Committee (PADAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee meeting to be held December 10, 2015. The purpose of the joint AC meeting is to discuss the safety of codeine-containing products in children and for FDA to obtain advice on whether codeine use in children should be restricted beyond the current contraindication in pediatric patients, post tonsillectomy and/or adenoidectomy, and whether codeine should remain available over the counter.

At the center of this review is the analysis of a series of 64 serious respiratory depression cases, from the FDA Adverse Event Reporting System (FAERS) data from 1965 to 2015, in children who had used a codeine-containing product. The majority of the 64 cases were in patients under 12 years old. The most frequently reported codeine-containing product was acetaminophen with codeine. Products containing promethazine with codeine were the primary products involved in the cough and cold setting. A temporal relationship was observed, with the adverse events occurring as early as after one dose of a codeine-containing product. There were 24 death cases in the FAERS case series. Twenty-one of 24 death cases involved children less than 12 years old, including 12 that reported use of a codeine-containing product for reasons other than pain management following tonsillectomy and/or adenoidectomy. As for risk factors in these serious and sometimes fatal cases, the information on CYP2D6 genotyping is limited. It was noted that there were death cases that involved patients who were either extensive (i.e., normal) metabolizers or ultra-rapid metabolizers of codeine.

The other epidemiological data sources examined for this review show modest-moderate levels of adverse effects from use of codeine-containing products in children. The National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project, which collects data from 63 hospitals on emergency department (ED) visits for adverse drug events (ADEs), contains, for years 2004-2013, 261 pediatric ED visit case reports for all codeine-containing **analgesic** products. Fourteen of these were for adverse reactions in patients 2-18 years of age given a codeine product for tonsillectomy pain. The NEISS-CADES also contains 73 pediatric ED visit reports for codeine-containing **cough and cold** products, with more than half the visits for children < 6 years of age. A majority of the 73 cases were the result of accidental or unintentional exposure, nine the result of an adverse effect, and 24 for allergic reactions. Cases resulting in death are not captured in this data.

The published national estimates of ED visits resulting from an adverse drug reaction (ADR) involving a codeine-containing medication, from SAMHSA's Drug Abuse Warning Network (DAWN) for 2004-2011, showed modest-moderate levels. The ADR category includes ED visits in which an adverse health consequence (e.g., side effect or an allergic reaction) resulted. The national estimates of ED visits for ADRs for codeine-containing **cough and cold** products in the pediatric population were not published due to estimate imprecision from small case counts, but national estimates were available for some years and pediatric age groups for ADR ED visits related to codeine-containing **analgesic** products. For children 0-5 years of age, the national estimate for codeine-involved analgesic ADR ED visits was 542 in 2008 and 853 in 2009. For children 6-11 years of age, this national estimate ranged

from 822 in 2006 to 1,342 in 2009. For children 12-17 years of age, these national estimates ranged over 2004-2011 from a low of 609 in 2008 to a high of 1,707 in 2009. Although these estimates vary in absolute value, they do not differ significantly in statistical terms. Nevertheless, these DAWN estimates show modest-moderate levels of analgesic codeine-product related pediatric ADR cases serious enough to present at an emergency department, but the data do not provide details on the seriousness of the case.

The utilization data show declines in both OTC and outpatient retail pharmacy prescription codeine product-related measures. Compared to year 2010, U.S. retail OTC sales of codeine-containing cough and cold products decreased 85%, to 169,000 bottles/packages in 2014. From 2010-2014, the number of pediatric patients (0-18 years old) receiving dispensed prescriptions for any codeine-containing product decreased 40% to 1.9 million patients; of which, 56% were <12 years old and 45% were 12-18 years old. By drug class, 76% of these pediatric patients received analgesic codeine-containing products and 26% received codeine-containing cold/cough products in 2014.

Overall, OSE concludes that there is some case report evidence of respiratory depression, sometimes resulting in death, following the use of codeine-containing products for both pain and cold/cough treatment, particularly in the pediatric population less than 12 years of age. Although a decrease in both OTC and pediatric prescription use of codeine-containing products was observed, 1.9 million pediatric patients received codeine-containing prescriptions from outpatient retail pharmacies in 2014. Although small in number, the FAERS cases of pediatric deaths with respiratory depression after codeine-containing product exposure occurred when the products were used not only for pain management following tonsillectomy and/or adenoidectomy, but also for other pain management and for cold/cough management. The FAERS, NEISS-CADES, and DAWN case data largely cannot be used to generate reliable national estimates, and the demonstrated levels of adverse effects and emergency department visits for children exposed to codeine products appear only modest-moderate. However, given the high pediatric use, these data do raise concern and interest in consideration of further regulatory action to promote safer use of codeine products in the pediatric population.

1 INTRODUCTION

1.1 BACKGROUND

The PAD and DSaRM advisory committees will discuss the safety of codeine products in children 18 years of age and younger. Codeine, often in combination with acetaminophen, is used for the treatment of pain in children, but it is contraindicated for pain after tonsillectomy or adenoidectomy. Codeine, in combination with other medicines, is also used for the relief of cough associated with upper respiratory allergies or the common cold in children. Codeine is available by prescription and also over the counter (through the OTC Drug Monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products). The focus of the meeting will be the risk of serious adverse events, such as respiratory depression and death, including reports in children who are CYP2D6 ultra-rapid metabolizers of codeine. FDA is interested in the advisory committees' views on whether the use of codeine in children should be restricted beyond the current contraindication for treatment of pain post tonsillectomy/ adenoidectomy and, if so, for what ages, and whether codeine should be available OTC.

Codeine is an opioid analgesic indicated for the relief of mild to moderately severe pain. Codeine has also been used for its antitussive effects in cough and cold preparations. Codeine is a prodrug whose metabolism to the active metabolite morphine depends on the cytochrome P450 isoenzyme 2D6 (CYP2D6) pathway. Age and genetic variants of CYP2D6 activity can affect codeine metabolism. CYP2D6 activity increases after birth. At birth, CYP2D6 activity is less than 1% of adult values, and before 5 years of age, CYP2D6 activity may be less than 25% of adult values.[1] In short, the ability to metabolize codeine increases with age and a person's metabolism rate affects the level of morphine in his/her blood. Furthermore, a large number of genetic variants exist for CYP2D6, and individuals are typically classified as poor metabolizers (PM), intermediate metabolizers (IM), extensive metabolizers (EM, i.e. normal), or ultra-rapid metabolizers (UM). Approximately 5-10% of a codeine dose is metabolized to morphine in patients who are CYP2D6 extensive metabolizers. [2] However, in patients who are CYP2D6 ultra-rapid metabolizers, their exposure to morphine is 1.5 times higher than for extensive metabolizers. [3]

The safety of codeine use in children has been a concern for years, particularly the risk of respiratory depression and death as well as the variability in metabolism of codeine. Over the past decade, FDA has updated the product label for codeine. In 2007, codeine labels were updated with information regarding variable metabolism and the risk of respiratory depression, particularly in infants of nursing mothers who used codeine. In 2012, FDA issued a Drug Safety Communication about reports of death and respiratory depression in pediatric patients, primarily with the use of codeine following tonsillectomy and/or adenoidectomy.[4] In 2013, FDA required a Boxed Warning and Contraindication for the use of codeine in this setting. [5]

In April 2015, the European Medicines Agency (EMA) completed a review of the use of codeine for cough and cold indications. The EMA contraindicated the use of codeine in children below 12 years of age for cough and cold, and they recommended that codeine not be used in children and adolescents between 12 and 18 years old who have breathing problems.[6]

Subsequent to the EMA's April 2015 additional contraindications for codeine use in children, FDA/DPARP reopened this tracked safety issue (TSI 1319) to review the safety of codeine-containing cough/cold products, as well as codeine combination analgesic products in children, and decided to

convene an AC meeting to discuss the available safety data with codeine use in children and to obtain advice on whether the use of codeine in children should be restricted beyond the current FDA contraindication and whether codeine should be available through the OTC Drug Monograph. In support of these discussions, DPARP requested that the Office of Surveillance and Epidemiology (OSE) provide a review of the following:

- the FDA Adverse Event Reporting System (FAERS) data for serious adverse events (SAEs) with all codeine-containing products in the pediatric population,
- the EMA Pharmacovigilance Risk Assessment Committee (PRAC) report to identify additional relevant cases,
- Literature regarding safety of codeine use as an antitussive or as an analgesic,
- Utilization of codeine cough/cold combination products, both prescription and through monograph (Rx and OTC)
- NEISS-CADES data for emergency department visits involving codeine-containing cough/cold and analgesic products and assessment of Poison Control Center data, if appropriate.

1.2 REGULATORY HISTORY

Codeine is an opioid analgesic indicated for the relief of mild to moderately severe pain where the use of an opioid analgesic is appropriate. It is also an active ingredient in cough/cold products. Because codeine is metabolized to morphine, high exposure to morphine occurs in patients who are ultra-rapid metabolizers.

In August 2007, the FDA issued a Public Health Advisory (PHA) to inform healthcare professionals, nursing mothers who are taking codeine, and ultra-rapid metabolizers regarding the risk of morphine overdose in their nursing infants. [7]

In August 2012, the FDA issued a Drug Safety Communication (DSC) regarding the use of codeine-containing products in certain children after tonsillectomy and/or adenoidectomy and the risk for rare, but life-threatening adverse events or death. [8] This communication was issued after three pediatric deaths and one non-fatal but life-threatening case of respiratory depression were documented in the medical literature. The Division of Pharmacovigilance-II (DPV-II) in OSE also completed a review evaluating pediatric deaths and overdoses associated with codeine use.[9]

In February 2013, the FDA asked the sponsors of codeine or dihydrocodeine containing products to update the Boxed Warning, Contraindication, Warnings/Precautions, Pediatric Use, and Patient Counseling Information labeling sections of their respective products to provide new safety information on the risk of serious adverse events or death associated with the use of codeine or dihydrocodeine containing products for pain relief after tonsillectomy and/or adenoidectomy. This request came after a safety review revealed that many serious adverse events or deaths occurred in children with obstructive sleep apnea who received codeine after a tonsillectomy and/or adenoidectomy. Due to the difficulty in determining which children are ultra-rapid metabolizers of codeine, it was contraindicated in all children within this setting.[10]

In April 2015, the EMA contraindicated the use of codeine-containing products for cough and cold indications in children less than 12 years of age, and limited the use in children and adolescents (ages 12-18) with a history of breathing problems. A completed review cited several published literature

case reports of respiratory depression and codeine intoxication in children related to the treatment of cough.[11]

In July 2015, the FDA issued another DSC regarding the risk of respiratory depression associated with the use of codeine to treat coughs and colds in children less than 18 years of age.[12]

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

2.1.1 *Determining Settings of Care*

Based on IMS Health, IMS National Sales Perspectives™, approximately 65% of bottles/packages of all cough/cold and analgesic codeine-containing products were distributed to outpatient retail pharmacies in 2014. About 34% and <1% of bottles/packages were sold to non-retail settings and mail-order/specialty settings, respectively, in 2014.[13] As a result, OTC sales and outpatient retail pharmacy utilization patterns of cough/cold and analgesic codeine-containing products were examined. Utilization patterns of cough/cold and analgesic codeine-containing products in the mail-order/specialty and non-retail pharmacy settings were not included in this review.

2.1.2 *Data Sources Used*

Proprietary databases available to the Agency were used to conduct the drug utilization analyses in this review (see Appendix A for full database descriptions).

Over-The Counter (OTC) Retail Sales to the Consumers

The IMS Health, OTC International Market Tracking (OTCIMS) database was used to provide national estimates of bottles/packages (units) of cough/cold codeine-containing products sold OTC from U.S. retail store outlets to the consumers from 2010 through 2014. No OTC data were captured for **analgesic** codeine-containing products as these are only available by prescription. These retail OTC sales data do not provide a direct estimate of patient use, but sales may be a surrogate for use, if we assume that drugs are purchased in quantities reflective of actual patient use. Furthermore, patient demographics are not available in this database because information on the end user of the product is unknown.

Data on Patients Who Received Dispensed Prescriptions

The IMS Health, Vector One®: Total Patient Tracker (TPT) database was used to provide national estimates of pediatric patients (0-18 years) who received prescriptions dispensed for cough/cold and analgesic codeine-containing products, stratified by patient age (0-1, 2-5, 6-11, and 12-18 years) and active ingredient, from U.S. outpatient retail pharmacies from 2010 through 2014. These patient analyses are inclusive of any indication. Furthermore, these patient analyses focus on only outpatient retail pharmacies. Therefore, these estimates may not apply to other settings of care such as mail-order/specialty and non-retail settings through/in which these products may be dispensed/used.

Prescriber Specialties

The IMS Health, National Prescriptions Audit™ database was used to provide national estimates of prescriptions dispensed for cough/cold and analgesic codeine-containing products, stratified by the top 10 prescriber specialties, from U.S. outpatient retail pharmacies from 2010 through 2014, cumulative.

Indications for Use

The Encuity Research, LLC., TreatmentAnswers™ with Pain Panel database was used to obtain the top 5 diagnoses (ICD-9-CM) associated with the use of cough/cold and analgesic codeine-containing products in the pediatric population (0-1, 2-5, 6-11, and 12-18 years) as reported by U.S. office-based physician surveys. These diagnoses data were obtained for year 2010 and year 2014 to provide insight into the utilization of these products for conditions related to tonsillectomy and/or adenoidectomy (ICD-9 474.x and 463), prior to, and after, the Drug Safety Communication (DSC) issued in 2012 and the addition of the Boxed Warning and Contraindication to codeine labeling in 2013.

2.2 RESULTS

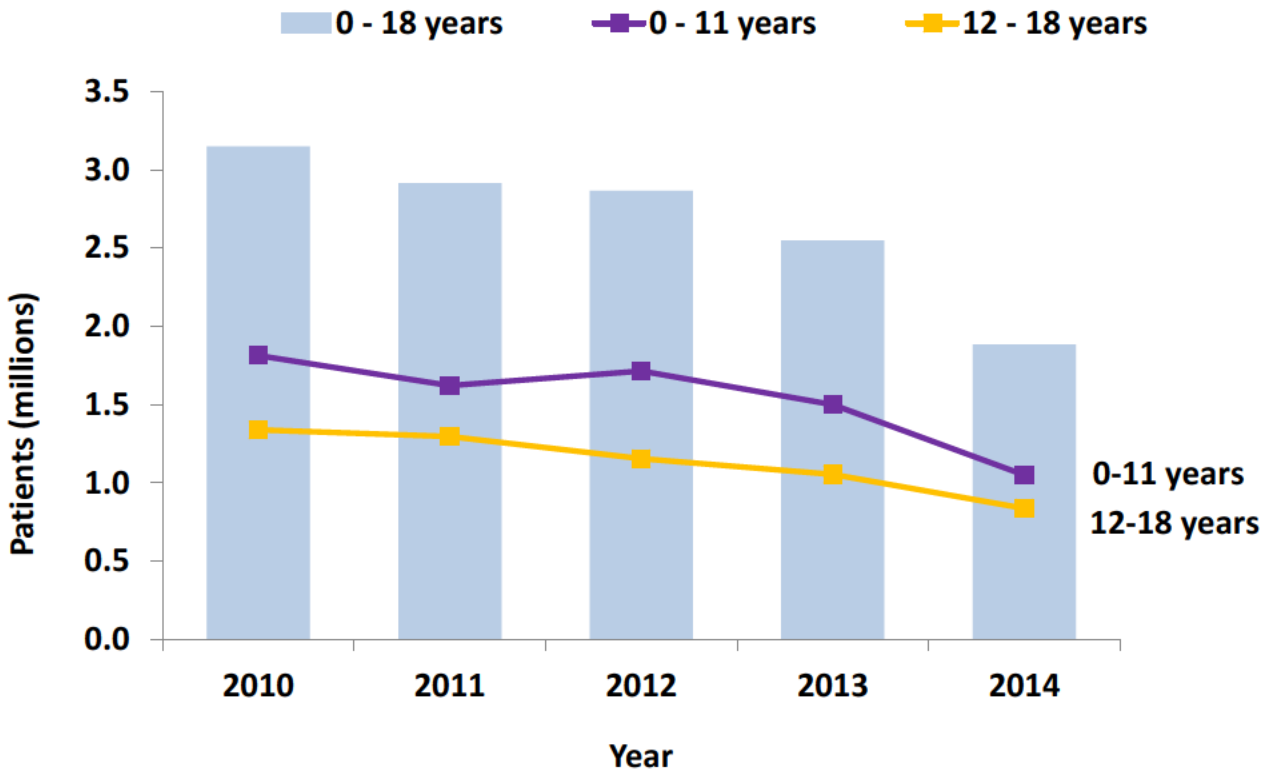
2.2.1 *OTC Retail Sales to the Consumers*

Table 2.3.1 in **Appendix B** provides national estimates of bottles/packages of cough/cold codeine-containing products sold over-the-counter to the consumers from U.S. retail store outlets. The number of bottles/packages of cough/cold codeine-containing products decreased by approximately 85% from 1.2 million bottles/packages sold in 2010 to 169,000 bottles/packages sold in 2014. Since 2012, combination codeine-guaifenesin accounted for the majority of total retail sales of cough/cold codeine-containing products at 61%-100%.

2.2.2 *Patient Demographics from Outpatient Retail Pharmacies*

The national estimates of pediatric patients (0-18 years) who received dispensed prescriptions for cough/cold and analgesic codeine-containing products by patient age from U.S. outpatient retail pharmacies are provided in **Table 2.3.2** in **Appendix B** and **Figure 2.3.1 below**. From 2010 to 2014, the total number of pediatric patients (0-18 years) who received dispensed prescriptions for codeine-containing products decreased by 40% from 3.1 million patients to 1.9 million patients. In 2014, about 1.1 million patients aged 0-11 years (56% of total pediatric patients) and 838,000 patients aged 12-18 years (45% of total pediatric patients) received codeine-containing products.

Figure 2.3.1. National estimates of pediatric patients (0-18 years) who received dispensed prescriptions for codeine-containing products by patient age from U.S. outpatient retail pharmacies, years 2010-2014

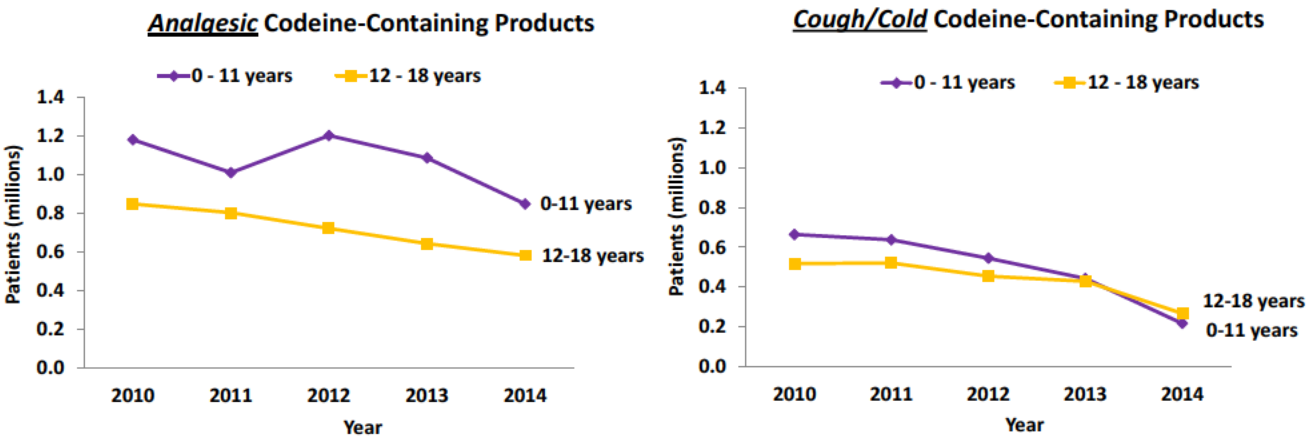


Source: IMS Health, Vector One®: Total Patient Tracker. Years 2010-2014. Data extracted June and August 2015.

The patient demographic data were also stratified by drug class (**Table 2.3.2** in **Appendix B** and **Figure 2.3.2 below**). The number of pediatric patients aged 0-18 years who received dispensed prescriptions for analgesic codeine-containing products decreased by 30% from 2 million patients (64% of total pediatric patients) in 2010 to 1.4 million patients (76% of total pediatric patients) in 2014. Meanwhile, the number of pediatric patients aged 0-18 years who received dispensed prescriptions for cough/cold codeine-containing products decreased by 59% from 1.2 million patients (38% of total pediatric patients) in 2010 to 483,000 patients (26% of total pediatric patients) in 2014.

There was a 67% decrease in the number of pediatric patients ages 0-11 years who received cough/cold codeine-containing products from 2010 to 2014, while there was a 49% decrease in patients ages 12-18 years for the same time. Unlike years 2010-2013, the number of pediatric patients aged 12-18 years (267,000 patients) who received dispensed prescriptions for cough/cold products was slightly higher than patients aged 0-11 years (217,000 patients) in 2014. Overall, the number of pediatric patients in all pediatric age groups and across both drug classes decreased during the examined time.

Figure 2.3.2. National estimates of pediatric patients (0-18 years) who received dispensed prescriptions for cough/cold and analgesic codeine-containing products by drug class and patient age from U.S. outpatient retail pharmacies, years 2010-2014



Source: IMS Health, Vector One®: Total Patient Tracker. Years 2010-2014. Data extracted June and August 2015.

Of those receiving analgesic codeine-containing products, over 99% of pediatric patients aged 0-18 years received prescriptions for combination codeine-acetaminophen products. Pediatric patients who received single-ingredient codeine products accounted for less than 0.5% of pediatric patients.
Of those receiving cough/cold codeine-containing products, approximately 52% of pediatric patients received combination codeine-guaifenesin products, followed by combination codeine-promethazine products at 42% of pediatric patients in 2014.

2.2.3 *Prescriber Specialties*

Table 2.3.3 in **Appendix B** provides the national estimates of prescriptions dispensed for analgesic and cough/cold codeine-containing products, stratified by the top 10 prescriber specialties, from U.S. outpatient retail pharmacies. Cumulatively, over the period 2010 through 2014, about 65.5 million and 60.1 million prescriptions were dispensed for analgesic and cough/cold codeine-containing products, respectively. Family Practice/General Practice/Doctor of Osteopathy was the top prescriber category, accounting for 24% of prescriptions dispensed for analgesic codeine-containing products and 43% of prescriptions dispensed for cough/cold codeine-containing products. Pediatricians accounted for only 2% of prescriptions dispensed for analgesic codeine-containing products (*data not shown in Table 2.3.3*) and 4% of prescriptions dispensed for cough/cold codeine-containing products.

2.2.4 *Indications for Use*

Table 2.3.4 and **Table 2.3.5** in **Appendix B** provide the top 5 diagnoses associated with the use of analgesic and cough/cold codeine-containing products, stratified by patient age, as reported from U.S. office-based physician survey data, in years 2010 and 2014. The top diagnoses associated with the pediatric use of analgesic codeine-containing products were conditions related to injuries and pain, while the top diagnoses associated with the pediatric use of cough/cold codeine-containing products were respiratory conditions. Of note, little to no use of analgesic or cough/cold codeine-containing

products was reported for conditions possibly related to tonsillectomy and/or adenoidectomy (ICD-9-CM codes 474.x and 463.x). The number of drug use mentions[a] for nearly all of the diagnoses associated with the use of analgesic and cough/cold codeine-containing products in the pediatric age subgroups were too low (<100,000 drug use mentions) to provide reliable annual national estimates and the determination of meaningful differences between these values was not possible.

3 POSTMARKETING ADVERSE EVENT REPORTS

3.1 SELECT CODEINE-CONTAINING PRODUCT LABELING [14]

The Boxed Warnings and Contraindications sections of the current labeling for promethazine with codeine[b] are reproduced below. See Appendix C for the Warnings, Precautions, Dosing and Administration, and Adverse Reactions sections of the product label.

BOXED WARNINGS

Respiratory Depression in Children: The combination of promethazine hydrochloride and codeine phosphate is contraindicated in pediatric patients less than 6 years of age. Concomitant administration of promethazine products with other respiratory depressants has an association with respiratory depression, and sometimes death in pediatric patients.

Post-marketing cases of respiratory depression, including fatalities, have been reported with use of promethazine hydrochloride in pediatric patients less than 2 years of age. A wide range of weight-based doses of promethazine hydrochloride have resulted in respiratory depression in these patients.

Death Related to Ultra-Rapid Metabolism of Codeine to Morphine: Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism. Deaths have also occurred in nursing infants who were exposed to high levels of morphine in breast milk because their mothers were ultra-rapid metabolizers of codeine.

CONTRAINDICATIONS

The combination of promethazine hydrochloride and codeine phosphate is contraindicated in pediatric patients less than 6 years of age, because the combination may cause fatal respiratory depression in this age population.

---

[a] Encuity Research, LLC uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

[b] Promethazine with codeine is one of the codeine-containing products for cough and cold indications that are available by prescription.

Codeine sulfate is contraindicated for post-operative pain management in children who have undergone tonsillectomy and/or adenoidectomy. (See **WARNINGS-Death Related to Ultra-Rapid Metabolism of Codeine to Morphine**).

Codeine is contraindicated in patients with a known hypersensitivity to the drug.

Antihistamines and codeine are both contraindicated for use in the treatment of lower respiratory tract symptoms, including asthma.

3.2 METHODS AND MATERIALS

A 2012 DPV-II review[15] of post-marketing reports identified the risk of respiratory depression resulting in death following the use of codeine-containing products for postoperative pain following tonsillectomy and/or adenoidectomy in the pediatric population. The EMA 2015 PRAC review additionally identified case reports with non-fatal serious outcomes. The current review evaluates post-marketing reports with fatal and non-fatal serious outcomes in the pediatric population, with a focus on: 1) respiratory depression, 2) respiratory distress, 3) designated medical events (DME)[c], and 4) substance abuse. Respiratory depression is presented in the main body of this review; please refer to Appendices H, I, and J for the other evaluations.

3.2.1 *Case Definition*

For the purpose of this review, DPV-I used the following case definition for respiratory depression:

3.2.1.1 **Respiratory Depression**

Case Inclusion Criteria

- Temporal association following a codeine-containing product administration

AND one of the following:

- Naloxone administration
- A diagnosis of respiratory depression
- Signs or symptoms consistent with respiratory depression, such as slow or shallow breathing, difficult or noisy breathing, or unusual sleepiness [16]
- Death outcome

Case Exclusion Criteria

- With strong alternative explanation(s)
- Suicidality (discussed in Appendix I)

[c] Designated Medical Events (DMEs) are adverse events that are considered rare, serious, and associated with a high drug-attributable risk and which constitute an alarm with as few as one to three reports. OSE created the DME list for working purposes; it has no regulatory significance. See Appendix G, Section 7.7.4 for a list of OSE's DMEs.

- Substance abuse (discussed in Appendix J)
- Transplacental exposure or breast feeding exposure
- Lack of information for proper assessment

3.2.1.2 **Additional Pediatric Searches**

- Respiratory Distress: because the clinical manifestations associated with respiratory compromise can encompass a spectrum of symptoms, we analyzed reports describing respiratory distress (see Appendix H).

- Designated Medical Events (DME): we evaluated reports describing DME to identify any new safety signals (see Appendix I).

- Substance abuse: The FAERS database does not adequately capture all reports of substance abuse; we expect overall under-reporting of abuse cases as well as incomplete capture of drug exposures in reported abuse cases. Nonetheless, we evaluated reports describing substance abuse in FAERS to gain qualitative information because DPARP was interested in the discussion on codeine misuse and dependence in adolescents in the EMA review (see Appendix J).

3.2.2 *FAERS Search Strategy*

3.2.2.1 **Respiratory Depression**

DPV-I searched the FDA Adverse Event Reporting System (FAERS) database for reports of pediatric cases of respiratory depression with codeine-containing products with a serious outcome, with the strategy described in Table 1.

Table 1. FAERS Search Strategy for Pediatric Reports of Respiratory Depression with Codeine-containing Products with a Serious Outcome*	
Date of search	May 26, 2015
Time period of search	January 1, 1965 – May 26, 2015
Search type	FBIS profile report
Outcome	Serious[†]
Product terms	Product active ingredient: acetaminophen/codeine phosphate, acetyldihydrocodeine hydrochloride, codeine, codeine hydrochloride, codeine phosphate, codeine phosphate anhydrous, codeine polistirex, codeine sulfate, dihydrocodeine, dihydrocodeine bitartrate, dihydrocodeine phosphate
MedDRA search terms (Version 18.0)	High Level Terms (HLTs): Breathing abnormalities, Respiratory failures, Death and sudden death, Tracheal therapeutics procedures, Disturbances in consciousness, Coma states, Conditions associated with abnormal gas exchange[††]
Age range	18 years of age and below

Table 1. FAERS Search Strategy for Pediatric Reports of Respiratory Depression with Codeine-containing Products with a Serious Outcome*
* See Appendix D for a description of the FAERS database. † Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. Reports may include multiple outcomes. †† See Appendix E for PT's associated with HLT search terms.

3.2.2.2 Additional Pediatric Searches

See Appendices H, I, and J for the search strategies for respiratory distress, DME, and substance abuse, respectively.

3.2.3 *Literature Search Strategy*

We searched the medical literature with the strategy described in Table 2. The literature search aims to identify case reports of adverse events with codeine-containing products in children or pediatric patients since the 2012 DPV review.

Table 2. Literature Search Strategy	
Date of search	July 16, 2015
Database	PubMed@FDA
Search terms	Codeine AND [children OR pediatric]
Years included in search	6/1/12* - 7/16/2015
*The dates included in the literature search were adjusted to capture any literature articles after the 2012 DPV review.	

3.3 RESULTS

3.3.1 *FAERS case selection*

3.3.1.1 Pediatric Reports of Respiratory Depression with a Serious Outcome

The FAERS search retrieved 243 reports based on the search strategy described in Section 3.2.2.1, Table 1. After applying the case definition from Section 3.2.1.1 and accounting for duplicate reports, 64 cases were included in the case series of respiratory depression reported with codeine-containing products in pediatric patients (see Figure 1).

Figure 1. FAERS Case Selection

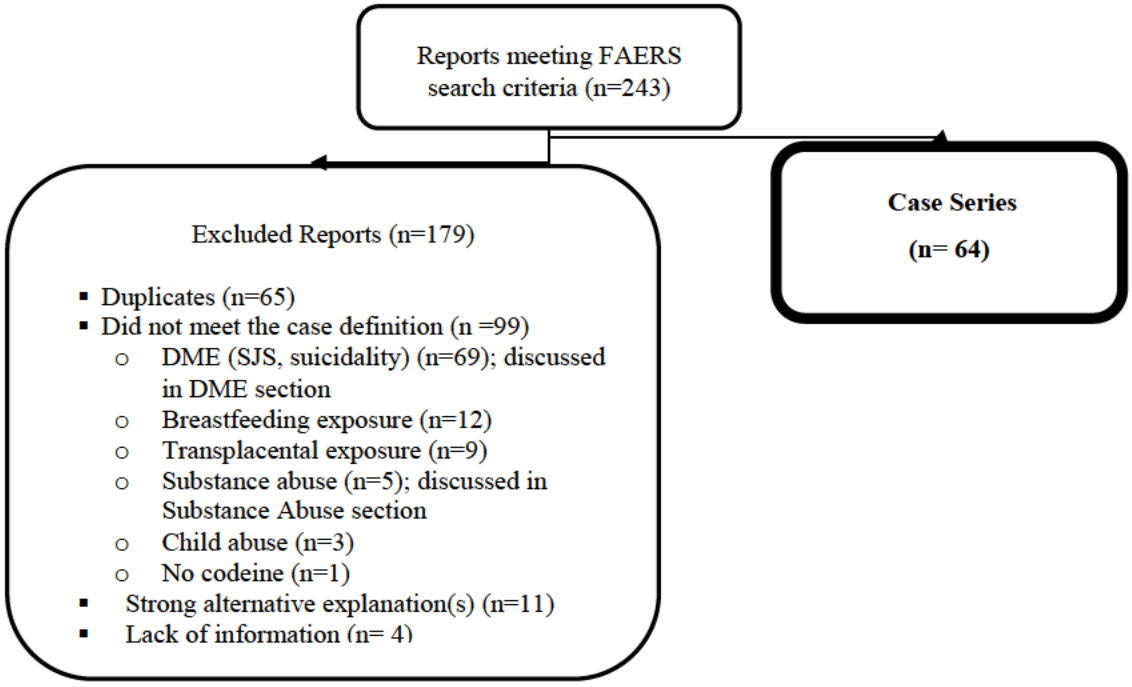


Table 3 summarizes important information about the 64 serious FAERS cases of respiratory depression in pediatric patients reported with codeine-containing products for this case series.

Table 3. Descriptive characteristics of serious pediatric FAERS cases of respiratory depression reported with codeine-containing products, received by FDA as of May 26, 2015 (N = 64)

Sex	Male	35
	Female	24
	Unknown	5
Age (years)	Mean	6
	Median	2.9
	Range	12 days – 17.21
	0-1 year	16
	2-5 years	23
	6-11 years	11
	12-18 years	14
Country	United States	41
	Foreign	23
Initial FDA Received Year*	1969-2012	42
	2013	9
	2014	11
	2015	2
Event Year*	1969-2012	33
	2013	4
	2014	1

Table 3. Descriptive characteristics of serious pediatric FAERS cases of respiratory depression reported with codeine-containing products, received by FDA as of May 26, 2015 (N = 64)		
	Unknown	26
Report Type	Expedited	44
	Direct	16
	Periodic	4
Time to event onset from start of therapy	Median	5 doses
	Range	1-18 doses
	1 dose	10
	2 doses	5
	3 doses	4
	4 doses	3
	6 doses	3
	10 doses	1
	12 doses	3
	18 doses	2
	Unknown	33
Codeine-Containing Products[†]	Acetaminophen with codeine	26
	Codeine unspecified	23
	Promethazine, phenylephrine with codeine	5
	Promethazine with codeine	5
	Guaifenesin with codeine	2
	Chlorpheniramine, phenylephrine with dihydrocodeine	1
	Triprolidine, pseudoephedrine with codeine	1
	Aspirin with codeine	1
	Dihydrocodeine unspecified	1
Serious Outcomes[‡]	Death	24
	Cough and cold use	7
	Post tonsillectomy and/or adenoidectomy	7
	General pain	2
	Other postoperative pain	2
	Sore throat/tonsillitis pain	2
	Dental pain	1
	Unknown use	3
	Hospitalization	21
	Life-threatening	16
	Disability	2
	Other Serious	30
Preferred Terms (Top 10)	Respiratory Depression	13
	Apnoea	9
	Dyspnoea	9
	Unresponsive to Stimuli	8
	Death	7
	Pyrexia	7
	Toxicity to Various Agents	7
	Loss of Consciousness	6
	Vomiting	6
	Cyanosis	5

Table 3. Descriptive characteristics of serious pediatric FAERS cases of respiratory depression reported with codeine-containing products, received by FDA as of May 26, 2015 (N = 64)		
	Overdose	5
Reasons for Use	Pain	34
	Post tonsillectomy and/or adenoidectomy	17
	Other surgery	5
	General pain	7
	Sore throat/Tonsillitis	3
	Dental pain	2
	Unknown	16
	Cough and Cold	14
Mention of CYP2D6 Genotype	Without mention	54
	With mention	10
	Ultra-rapid metabolizer (UM)	7
	Extensive metabolizer (EM)	3
Codeine or morphine levels (n=15) [§]	Above therapeutic range	13
	Blood levels	2
	Postmortem	11
	Therapeutic range	2
	Blood levels	1
	Postmortem	1

[*] Reports received prior to the DSC issued by the FDA in 2012 were grouped together.
[†] Cases may contain more than one codeine-containing product.
[‡] Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. Reports may include multiple outcomes.
[§] There was one FAERS literature case that did not contain levels within the report; however, levels were obtained from the literature article.

Key findings from the 64 pediatric cases of respiratory depression include the following:

- Fifty cases involved children under the age of 12; the median age was 2.9 years, ranging from 0.03 to 17.21 years.
- Thirty-eight cases provided the date on which the adverse event occurred; one of 38 cases reported respiratory depression in the setting of pain management following tonsillectomy and/or adenoidectomy after August 2012 (FDA DSC date).
- Thirty-one cases provided information on time-to-event onset (TTO); TTO ranged from one to 18 doses, from the start of therapy, and the median TTO was five doses.
- The most frequently reported codeine-containing product was acetaminophen with codeine (n= 26). Promethazine with codeine (with and without phenylephrine) was the most frequently reported codeine-containing product in the cough and cold setting.
- Among the 48 cases that reported the reason for use, 34 reported pain management and 14 reported cough and cold management.
- Twenty-four cases reported a death outcome; 21 deaths occurred in children less than 12 years of age. Twelve of the 21 deaths in patients under 12 years old occurred when a codeine-containing product was used unrelated to pain management following tonsillectomy and/or adenoidectomy: for cough and cold (n=7), general pain (n=2),

postoperative pain not associated with tonsillectomy and/or adenoidectomy (n=2), and sore/strep throat pain (n=1).

- Ten cases mentioned CYP2D6 genotype; seven patients were ultra-rapid metabolizers, and three patients were extensive metabolizers. The remaining 54 cases did not report CYP2D6 genotyping.
- Fifteen cases reported codeine or morphine levels; 13 cases were above the therapeutic range, and two cases were within the therapeutic range. Among the two cases that reported therapeutic levels, one had a death outcome within the setting of pain management following tonsillectomy and/or adenoidectomy. The remaining 49 cases did not report codeine or morphine levels.

Sample Respiratory Depression Cases in the Cough and Cold Setting

FAERS Case # 6959752 and 6959806, Foreign, Death and Hospitalization, 2012: This is a literature report[17] involving two monozygotic 3-year-old twins who developed respiratory depression 6 days after codeine administration for an upper respiratory tract infection. The mother administered to each child 10 drops (12.5mg) of codeine daily (for six days) instead of the recommended 0.5ml (10mg) of codeine daily. Twin 1 was found apneic and lying in vomit by his mother, and emergency services was called. Upon admission to the hospital, Twin 1 was in a coma and required ventilation but eventually recovered. Two and a half hours after the mother called emergency services for Twin 1, Twin 2 was found lying in vomit and dead by his father. Both twins were found to be extensive[d] (i.e. normal) metabolizers (EM) of codeine. Serum codeine and morphine levels for Twin 1 were drawn 6 hours after the last dose and found to be in therapeutic range, while post-mortem serum codeine and morphine levels for Twin 2 were within the lethal range. The authors commented that the variability of codeine dosage administered by a dropper, in combination with the accumulation of codeine over 6 days, may have contributed to the opiate intoxication in both twins. Despite having therapeutic serum levels of codeine and morphine, Twin 1 still experienced respiratory depression and required medical intervention with ventilation.

Reviewer comment: Both twins were found to be extensive metabolizers of codeine; however, the twins experienced different clinical outcomes and had vastly different serum codeine and morphine levels.

FAERS Case # 9379348, US, Death, 2013: This is a literature report[18] involving an overweight 6-year old girl who was prescribed guaifenesin with codeine for severe cough and respiratory infection. There was an inadvertent prescription labeling error of 1-2 teaspoons every 4 hours as needed, instead of 1-2 teaspoons at bedtime. The child received three doses of guaifenesin with codeine and went to bed after the last dose. Forty-five minutes after the last dose, the mother noted her child to be a "little bit blue" and called the hospital emergency department (ED) for assistance. The ED informed the mother that her daughter might be hypoxic and advised her to bring the child to the ED. The mother did not follow the advice of the ED and the following morning the child was found dead. Resuscitation efforts were unsuccessful. Postmortem examination revealed cerebral edema. The hepatic blood codeine level was 0.13mg/kg, and the morphine level was 0.16mg/kg; both levels were within the toxic range. Other medical history included myocarditis, developmental delay, and obesity. The patient also had received azithromycin concomitantly.

[d] Extensive metabolizers have normal CYP2D6 function.

Reviewer comment: The patient received a higher dose of codeine because of the labeling error. Although the administered dose was still within the recommended antitussive dose (0.5-1mg/kg/dose every 4 hours as needed), the patient's codeine and morphine levels were in the toxic range. The patient's CYP2D6 status was unknown. Azithromycin is labeled for the risk of QT prolongation and Torsades de Pointes and may also have contributed to the patient's clinical course.

FAERS Case # 4746652, US, Death, 1990: This is a literature report[19] involving a 4-year-old female who had velopharyngeal flap reconstruction to correct her hypernasal speech. The patient was noted to have obstructive sleep apnea several hours after her surgery, but she was subsequently discharged home on postoperative day 8 when she had no other episodes of sleep apnea. Four weeks after the surgery, the patient developed a fever and began to cough. She was treated with aspirin and sponging and was given two doses of 1 & ½ teaspoons of a "cough mixture." Each dose was estimated to contain 7.5mg of promethazine and 15mg of codeine. She was found dead the next morning by her mother. Autopsy results revealed patchy areas of bronchopneumonia. Other pertinent medical history included: velo-cardio-facial syndrome and surgical repair of cleft palate 2 years ago.

Reviewer comment: Although the patient's cause of death was not provided, this case met the case definition of respiratory depression. It is unknown if the patient had supra-therapeutic codeine and morphine levels. The patient had respiratory risk factors, including obstructive sleep apnea, that may have been a contributing factor in the patient's death. The current product label for promethazine with codeine contraindicates use in pediatric patients less than 6 years of age.

Sample Respiratory Depression Cases in the Analgesic Setting

Post Adenoidectomy and/or Tonsillectomy

The majority of the respiratory depression cases in this setting were discussed in a prior 2012 DPV-II review. See the 2012 DPV-II review for additional representative cases.[20]

FAERS Case # 10280898, US, Death, 2014: A 2-year-old male underwent a tonsillectomy, adenoidectomy, and myringotomy and was discharged home with a prescription for acetaminophen with codeine for pain. The patient received 2 doses of acetaminophen with codeine and he was found to be lethargic, listless, and "doped up" approximately 2 hours after the last dose was administered. He was brought to his physician's office for further evaluation, where he subsequently coded and died. Autopsy findings included marked bronchopneumonia. Cardiac blood levels were: acetaminophen 6.5mcg/mL, free codeine 190ng/mL, and free morphine 19ng/ml. The medical examiner noted that the serum levels of acetaminophen, codeine, and morphine were "non-contributory and within therapeutic limits." Cardiac evaluation at autopsy found mild right ventricular enlargement, left atrial enlargement, mild left ventricular hypertrophy, and right atrial enlargement. Other pertinent medical information included history of tonsillitis, obstructive sleep apnea, chronic otitis media, and partial hearing loss. Other concomitant medication included albuterol sulfate.

Reviewer comment: It was reported that the patient's codeine and morphine levels were within therapeutic range. The patient appeared to have several confounding respiratory and cardiac risk factors (such as obstructive sleep apnea, bronchopneumonia, and cardiomyopathy) that in combination with the administration of a codeine-containing product may have contributed to the

patient's clinical course. This case was received in FAERS after the posting of the DSC and labeling update contraindicating the use of codeine for pain management following tonsillectomy and/or adenoidectomy (event date reported was summer 2013).

Other Post-operative Surgery

FAERS Case # 9382047, US, Death, 2013: This is a literature report[21] of a 10-year-old overweight girl of Guatemalan descent who underwent orthopedic surgery for bilateral hip subluxation and developed respiratory depression following codeine administration. Five days after her surgery, she was discharged home with prescriptions for acetaminophen with codeine liquid (20-40mg of codeine) every 4 hours for pain and diazepam 2-4 mg every 4 hours as needed for spasms. She received one dose of acetaminophen with codeine in the afternoon and another dose at bedtime along with the diazepam. When the mother tried to wake the child, she was cold and unresponsive. Resuscitation efforts were unsuccessful. Postmortem codeine and morphine blood concentrations were in the toxic range. The patient's significant past medical history included cerebral palsy, reactive airway disease, and "snoring and enlarged tonsils."

Reviewer's comment: The combined sedative effects of codeine and diazepam likely caused respiratory depression, and the patient's history of "snoring and enlarged tonsils" and reactive airway disease were potential contributing factors in the patient's death. This is a death case where codeine was used in a setting that is not mentioned in the current codeine labeling.

General Pain

FAERS Case # 9397006, Direct US, Hospitalization, 2013: A 13-year-old female of African American descent took acetaminophen with codeine (30 mg) for pain associated with sickle cell disease. After one dose of acetaminophen with codeine, the patient's mother noted that the patient experienced extreme drowsiness and was difficult to arouse. The patient had previously taken acetaminophen with codeine many years ago and experienced drowsiness at that time as well. The patient underwent genetic testing and was found to be an ultra-rapid metabolizer (UM) of CYP2D6. No other past medical history was noted.

Reviewer comment: Drowsiness is a labeled adverse event for acetaminophen with codeine. The temporal relationship between the administration of acetaminophen with codeine and the symptoms of drowsiness are consistent with the labeling. This case lacked additional clinical information. The patient only received one dose of acetaminophen with codeine and was difficult to arouse; her ultra-rapid metabolizer status and her age may explain the severity of her symptoms.

Dental Pain

FAERS Case # 8749396, US, Death, 2012: A 14-year-old male was prescribed acetaminophen with codeine for jaw pain and pain related to a tooth abscess. He received a total of six doses of acetaminophen with codeine over two days and went to bed after his last dose and was noted to be snoring. The following morning he was found unresponsive and apneic in bed. The patient was declared dead one hour later. Autopsy revealed a femoral blood level of morphine = 11.8 ng/ml and codeine = 117 ng/ml. Urine levels of drugs were the following: morphine = 5069 ng/ml, codeine

>10,000 ng/ml, and hydrocodone = 57 ng/ml. Other pertinent past medical history included attention deficit disorder, oppositional/defiant disorder, physical and verbal aggression, and self-harm inflicted by chewing on his hands. Concomitant medications included quetiapine, sertraline, valproic acid, clonidine, aripiprazole, diphenhydramine, meloxicam, penicillin, and lisdexamfetamine.

Reviewer comment: Both codeine and morphine blood levels in this patient were considered to be in the toxic range. [22] This is a death case where codeine was used in a setting that is not mentioned in the current codeine labeling.

Sample Respiratory Depression Case for Unknown Use

FAERS Case # 5967315, US, Hospitalization 2006: This is a literature report[23] of an 8-month-old preterm infant with Pierre-Robin syndrome who was admitted to the Pediatric Intensive Care Unit following an "acute life-threatening event" at home. A new onset fever was noted on the morning of admission and the patient was inadvertently given 2 ml of acetaminophen with codeine (4.8 mg of codeine) instead of acetaminophen for the fever. The patient had some acute changes in mental status and was found to be hypotonic, apneic, and cyanotic. The mother performed rescue breathing for 10 minutes prior to the arrival of an ambulance. Upon admission, the patient was breathing spontaneously but continued to be hypotonic with decreased responsiveness. After a few hours of mechanical ventilation, the patient became responsive and interactive. The patient was hospitalized for 6 days for the treatment of pneumonia and respiratory distress. Other pertinent medical history included Pierre-Robin syndrome, recent tracheostomy and gastrostomy tube placement, and a two day history of cough and increased secretions. The author commented that the dose of codeine (4.8 mg or 1.3 mg/kg) that the patient received was not "excessively greater" than the usual therapeutic dose of 0.5-1 mg/kg. The author further indicated that infants may be at increased risk of respiratory depression for several reasons, including alterations in the permeability of the blood-brain barrier, immaturity of the central respiratory control centers, and altered metabolism due to immaturity of the hepatic microsomal enzymes.

Reviewer comment: The patient received acetaminophen with codeine inadvertently. This patient had respiratory risk factors that included Pierre-Robin syndrome and recent tracheostomy placement that may have been contributing factors to the patient's respiratory depression. This is a case where codeine was used in a setting that is not mentioned in the current codeine labeling.

See Appendix G for additional sample narratives.

3.3.2 *Additional Pediatric Searches*

- Respiratory Distress: most reports involved overdose related to polysubstance abuse or abnormal behavior (such as hallucinations and delirium) associated with influenza, promethazine or in combination with antipsychotics or other opioids. (See Appendix H for additional details)

- Designated Medical Events: there were no new safety signals identified. (See Appendix I for additional details)

- Substance Abuse: most reports described concurrent use of benzodiazepines, antidepressants or other opioids. (See Appendix J for additional details)

3.3.2.1 **Literature Search**

The literature search, based on the search strategy in Table 2, Section 3.2.3, retrieved 59 articles. One of 59 articles involved three case reports of adverse events with codeine-containing products. Friedrichsdorf et al[24] described the deaths of three children ages 4-10 years old from codeine toxicity. One case that was reported in the literature is summarized below. Please see Section 3.3.1.1 (Pediatric Reports of Respiratory Depression with a Serious Outcome) for a summary of the other two cases that describe codeine use as a cough suppressant and for pain management after orthopedic surgery.

Case 1 involved a 4-year-old morbidly obese girl who had a tonsillectomy/adenoidectomy without complications and developed respiratory depression following codeine administration. After her surgery, she was discharged home with a prescription for acetaminophen with codeine liquid (12-17mg) every 4 hours as needed for pain. She received a total of 4 doses, went to bed after the last dose, and was found unresponsive the following morning. Resuscitative measures were unsuccessful. Postmortem exam revealed no anatomic cause of death. Additional CYP2D6 testing found the patient to have an extensive metabolizer (normal) phenotype. The death was declared an accident attributable to codeine toxicity. The patient's other significant medical history included a traumatic brain injury 2 years prior which resulted in speech delay and left hemiparesis and a history of absence seizures that were controlled with valproate.

The authors stated that all three children were overweight or obese; however, the codeine doses were within recommended dose ranges for adjusted lean weight. They further commented that codeine should not be recommended for children due to the poor analgesic effect and occasional risk of opioid toxicity and oversedation.

4 EPIDEMIOLOGICAL DATA

4.1 METHODS AND MATERIALS

In addition to the National Electronic Injury Surveillance System (NEISS-CADES) dataset, DEPI examined the Drug Abuse Warning Network (DAWN) and the National Poison Center (NPDS) Annual Reports to explore if these sources could provide informative data on serious adverse events associated with codeine-containing cough/cold or analgesic products in children. The NPDS data, presented aggregated in tables in annual reports, was not informative so it is not discussed below. A comprehensive search for epidemiologic studies was conducted as well.

4.1.1 Literature Search

Using the National Library of Medicine's MEDLINE® database PubMed search engine, DEPI conducted a comprehensive literature search for studies containing epidemiologic data on serious adverse events associated with codeine-containing cough and cold as well as analgesic products in the pediatric population. The search included all available years. Experimental studies, case series

reports, studies that related specifically to drug misuse/abuse, and articles pertaining only to countries outside the U.S. were excluded.

Table 4.2.1. Literature Search Strategy	
Date of search	September, 10, 2015
Database	PubMed@FDA
Search terms	Codeine AND epidemiology AND (children OR pediatric)
Years included in search	All available

4.1.2 *Drug Abuse Warning Network (DAWN)*

The Drug Abuse Warning Network (DAWN), administered by the Substance Abuse and Mental Health Services Administration (SAMHSA), was a public health surveillance system that collected data from 2004 through 2011 on drug-related emergency department (ED) visits DAWN captured all drug-related ED visits not just those related to drug abuse. Hospitals eligible for DAWN included non-federal, short-stay, general and surgical hospitals that operated 24-hour EDs. The data from a national sample of hospitals (233 participating hospitals in the US) were collected by retrospective review of medical records. National estimates of ED visits were generated after adjustments and weights were applied to the aggregate data submitted by these sampled hospitals. However, estimates with a relative standard error >50% or an unweighted count or estimate <30 were suppressed. Estimates from DAWN include estimates of ED visits due to an adverse drug reaction (ADR). This analytic category includes ED visits in which an adverse health consequence (e.g., side effects or an allergic reaction) resulted when taking prescription drugs, over-the-counter medications, or dietary supplements as prescribed or as recommended. The national annual estimates for ADR ED visits involving either codeine-guaifenesin or codeine-promethazine products, ranged between 900 and 2,300 for each year between 2004 and 2011. However, the national annual estimates in patients 0-18 years of age were suppressed. As a result, only national estimates involving **analgesic** codeine combination products in the pediatric population are presented from DAWN in this review.

4.1.3 *National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES)*

The National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project collects data on ED visits for adverse drug events (ADEs) in the outpatient setting. The NEISS-CADES project is a joint effort of the CDC, the U.S. Consumer Product Safety Commission, and the U.S. Food and Drug Administration and provides data from a national stratified probability sample of 63 hospitals with a minimum of six beds and a 24-hour emergency department (ED) in the U.S. and its territories. The NEISS-CADES project is described in detail elsewhere.[25,26,27] All the cases in NEISS-CADES are ED visits for a condition that the treating clinician explicitly attributed to the use of a drug or a drug-specific effect. Data are currently available for the period 2004-2013. Adverse drug events include allergic reactions, adverse effects, unintentional overdoses, or secondary effects (e.g. choking), but exclude intentional self-harm, drug therapeutic failures, drug withdrawal, and drug abuse. Follow-up visits for an ADE previously diagnosed and treated or ADEs occurring during the ED visit are also excluded, as are deaths due to ADEs. For each adverse event,

trained coders in participating hospitals record narrative descriptions of the incident, including patient symptoms and clinician diagnoses, and report up to two medications implicated in the ADE.[e]

DEPI examined the NEISS-CADES dataset to identify pediatric patients' (up to 18 years of age) emergency department (ED) visits associated with codeine-containing products and determined that these data were informative. These data provide clinical information on ED visits that are both pertinent to pediatric patients and to the substance of interest, codeine-containing cough and cold and analgesic products. Unspecified cases that were found as "unspecified codeine-containing cough and cold products," were identified via an individual review of the case narrative. These were the result of examining cases that were listed as "COUGH COLD REMEDIES, NARCOTIC, NOS". After reviewing these cases, it was determined that 14 involved a codeine-containing cough/cold product that was included in the analysis. Due to the low number of events, national estimates of these events could not be computed.

4.1.3.1 Selection of NEISS-CADES Cases

Cases considered for this review reported use of codeine-containing cough and cold and analgesic products among pediatric cases 0 to 18 years of age. Cases were examined and categorized by drug substance and by adverse drug event (ADE) mechanism. M. Lovegrove of the Centers for Disease Control and Prevention Medication Safety Program performed the NEISS-CADES search for FDA. The details of the search strategy are shown in Table 4.1.3.1.

Table 4.1.3.1: NEISS-CADES Search Strategy

Data Timeline	January 1, 2004 - December 31, 2013
Search Term: Generic Names	
Cough and Cold Remedies	CODEINE/GUAIFENESIN
	CODEINE/GUAIFENESIN/PSEUDOEPHEDRINE
	CODEINE/PROMETHAZINE
	COUGH COLD REMEDIES, NARCOTIC,NOS**
Analgesics	ACETAMINOPHEN/CODEINE
	ASPIRIN/BUTALBITAL/CAFFEINE/CODEINE
	CODEINE*
Age Range	0 - 18 years

4.2 RESULTS

4.2.1 *Epidemiologic Literature Review Results*

[e] Additional medications can be recorded, but have fewer details on dose, route, and length of exposure.

DEPI identified one study that examined the use of codeine-containing products in the U.S. pediatric population and ADRs. This study, entitled **"Codeine-Related Adverse Drug Reactions in Children Following Tonsillectomy: A Prospective Study"** (Prows et. al, 2014)[28], is summarized here.

This study focused on over sedation or unusual sleepiness as its primary outcome, because the authors considered it an early warning sign of impending opioid-related respiratory depression, particularly in children with an obstructive sleep apnea (OSA) history. It was a post-hoc analysis of an observational prospective nested cohort pharmaco-epigenetic study, "Personalizing Perioperative Morphine Analgesia in Children." The study authors hypothesized that CYP2D6 genotype-predicted phenotype was associated with ADR occurrence. This genotype-predicted phenotype blinded clinical observational study in a population of children with acute pain was to determine factors associated with codeine's adverse effects after hospital discharge during postoperative days (PODs) 0 to 3 following tonsillectomy without or with adenoidectomy (T/TA.) Children aged 6–15 years were recruited from same-day surgery on the day of their elective T/A in Cincinnati Children's Hospital Medical Center. All races were included, as were children who required a T/TA because of obstructive sleep apnea (OSA). There were 249 children 6 to 15 years of age scheduled for tonsillectomy, enrolled and genotyped for the CYPD6 allele in this study. All children had tonsillectomy by electrocautery and received standard doses of intravenous (IV) morphine (0.2 mg/kg, except children with OSA who received 0.1 mg/kg), dexamethasone, and ondansetron during surgery. As this study occurred before the FDA alerts, treating surgeons prescribed an opioid (typically codeine) with acetaminophen compound in liquid form for pain as needed. Home diary data were obtained from 161 of the 249 patients and 134 of those with diary data met the inclusion criteria. Repeated adverse drug reaction (ADR) measures documented by parents at home were examined. This included a home data collection instrument score to measure sedation.

The association of CYP2D6-predicted phenotype with ADR and sedation was tested. The primary outcome was the sum of daily ADR events including dizziness, nausea, vomiting, dry mouth, itching, blurry vision, and rash. A total of 106 patients (79%) reported at least one ADR. The most common ADRs for white children were nausea, lightheadedness/dizziness and nausea, while vomiting was the most common for African American children. For genetic studies, it is standard practice to analyze racial groups separately, but because the proportion of nonwhite children was small and some phenotypes were missing in these groups, the authors restricted the final analysis to white subjects.

This study, found children with at least one full function CYP2D6 allele had a higher ADR risk when compared to children without a full function allele. In this sub-cohort of white children, $\leq$ 45 kg; increased ADR risk was associated with the presence of one or more full function CYP2D6 alleles ($P<0.001$). The risk was highest the evening after T/TA despite fewer doses of codeine. Limitations of this study include the small number of study participants as well as the institution's practice to advise parents only to use codeine as a rescue pain medicine and only on an as needed-basis that likely contributed to the lack of severe ADRs in this cohort. Nevertheless, the authors concluded that the study "results provide evidence that multiple factors are associated with codeine-related ADRs and supported the FDA recommendation to avoid codeine's routine use following tonsillectomy in children."[29]

4.2.2 *Drug Abuse Warning Network (DAWN) Results*

As stated previously, national estimates of ADR ED visits for codeine-containing **cough and cold** products in the pediatric population were not published in DAWN because these estimates did not meet the standards of data precision (e.g. the counts were too small). Table 4.2.2 provides the annual DAWN national estimates and confidence intervals, for the number of ADR ED visits from ingestion of codeine-containing **analgesic** products by age bands for years 2004 through 2011.

The national estimates of ADR ED visits related to codeine-containing analgesic products in children were variable in absolute terms, but had broad confidence intervals that largely overlapped and thus did not change significantly between years or age groups. For children ages 0-5 years of age, the ADR ED visit estimate was 542 (95% CI = 106, 979) in 2008 and 853 (95% CI = 233, 1,474) in 2009. Estimates for the other years were suppressed. Estimates for children 6-11 years of age ranged from 822 (95% CI = 120, 1,524) in 2006 to 1,342 (95% CI = 460, 2,223) in 2009. Estimates for 2010-2011 were suppressed. For children 12-17 years of age, the national estimates ranged over 2004-2011 from the low of 609 (95% CI = 220, 998) visits in 2008, to the high of 1,707 (95% CI = 734, 2,679) visits in 2009. Although these national estimates vary in absolute value, they have wide confidence intervals and do not differ significantly in statistical terms.

Table 4.2.2 DAWN 2004-2011: National Estimates of Adverse Drug Reaction ED Visits associated with Codeine-containing Analgesic products, by pediatric age group

DAWN: 2004-2011								
Codeine/combination Analgesics	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**
0-5 years	*	*	*	*	542	853	*	*
95% Confidence Intervals					106, 979	233, 1,474		
6-11 years	*	846	822	1,207	1,060	1,342	*	*
95% Confidence Intervals		328, 1,364	120, 1,524	202, 2,213	524, 1,597	460, 2,223		
12-17 years	841	653	1,520	984	609	1,707	1,043	1,073
95% Confidence Intervals	184, 1498	145, 1,161	781, 2,259	439, 1,530	220, 998	734, 2,679	398, 1,688	123, 2,023

* indicates figure does not meet standards of precision. Estimates with a relative standard error greater than 50% or an unweighted count or estimate less than 30 are suppressed.
Source: Center for Behavioral Health Statistics and Quality, SAMHSA, Drug Abuse Warning Network, 2011.

4.2.3 *NEISS-CADES Results*

Table 4.2.3.1 presents a summary of the NEISS-CADES ED visits by drug substance and age group during the entire study period, 2004 -2013. (These are counts, not national projections.)

There were 73 pediatric ED visits related to codeine-containing **cough and cold** products. Of those, 31 cases involved codeine/promethazine, 25 involved codeine/guaifenesin, 3 involved codeine/ guaifenesin/pseudoephedrine, and 14 cases were attributed to an unspecified codeine-containing cough and cold product. Fourteen ED visits related to exposure to cough/cold products involved children less than 2 years of age, 26 ED visits involved children 2-5 years of age, 11 visits involved 6-11 year olds and 22 involved 12-18 year olds.

For pediatric ED visits involving codeine-containing **analgesic** products, the number of pediatric ED visits was higher. There were 261 ED visits for all codeine-containing analgesic products. The majority of these ED visits (234 cases) was the result of acetaminophen/codeine ingestion, followed by single ingredient codeine (26 cases) and one ED visit for an aspirin/butalbital/caffeine/codeine product.

The largest proportion of ED visits due to codeine-containing analgesic products involved children 12-18 years of age, with 116 cases. The number of ED visits involving children less than 2 years of age was 32, and there were 56 and 57 ED visits for children 2-5 and 6-11 years of age, respectively.

Table 4.2.3.1 NEISS-CADES 2004-2013: Summary of Pediatric ED Visits for Codeine-containing Drug Products by Drug Substance and Age Group

NEISS-CADES 2004-2013					
Product	**Age Group (Years)**				
	<2	**2-5**	**6-11**	**12-18**	**Total**
Cough and Cold Products					
Codeine/Promethazine	7	13	5	6	31
Codeine/Guaifenesin	5	6	3	11	25
Codeine/Guaifenesin/Pseudoephedrine	0	2	0	1	3
Unspecified codeine-containing cough and cold products	2	5	3	4	14
Total	**14**	**26**	**11**	**22**	**73**
Analgesic Products					
Acetaminophen/Codeine	26	54	43	111	234
Codeine	5	2	14	5	26
Aspirin/Butalbital/Caffeine/Codeine	1	0	0	0	1
Total	**32**	**56**	**57**	**116**	**261**

*1 case reclassified as a codeine-containing cough and cold remedy based on narrative review
2 ED visits for injuries related to how a codeine-containing was taken were excluded from analysis (e.g., choking on a pill)

Table 4.2.3.2 summarizes the distribution of the ED cases by the adverse drug event "mechanism" that the physician identified as the reason for the ED visit. For ED visits involving **cough and cold** products, 13 ED visits were the result of accidental exposure or unintentional exposure among children less than 2 years of age and one from an allergic reaction. Among children 2-5 years of age, there were 19 ED visits that were the result of accidental or unintentional exposure, four cases were allergic reactions and three cases were the result of an adverse effect. Accidental/unintentional cases were the result of either the caregiver administering the wrong medication (i.e., giving promethazine with codeine liquid instead of Zantac) or the child was found with evidence of liquid ingestion in the absence of the caregiver (i.e., patient was found with codeine-containing cough and cold product on their t-shirt). Among the older age groups, there were proportionally fewer accidental exposures (4 cases for each age group) and proportionally more ED visits involving allergic reactions or adverse effect. There were 6 and 13 allergic reaction ED visits for children 6-11 and 12-18 years, respectively. Most allergic reaction visits involved rash, hives and in some cases tongue swelling. For ED visits involving adverse effect, there were five events involving children 12-18 years of age, 3 involving children 2-5 years of age and one visit for a child 6-11 years old.

For ED visits involving **analgesic** products, for children under 2 years of age, again the majority of ED visits (27 out of 32) involved accidental ingestion. For children 2-5 years of age, there were 29 visits as a result of accidental ingestion, 17 ED visits due to an allergic reaction and 10 ED visits due to an adverse effect. For children 6-11 years of age, there were four ED visits attributed to accidental ingestion, 34 ED visits as a result of an allergic reaction and 19 ED visits due to an adverse effect. For children 12-18 years old, 14 ED visits resulted from an accidental ingestion, 61 ED visits were for an allergic reaction and 41 ED visits were for an adverse effect.

Table 4.2.3.2 NEISS-CADES 2004 – 2013: Summary of Codeine-containing Cough and Cold ED Visits by Adverse Drug Event

Codeine-containing Cough and Cold Products				
Age Group	**Adverse Drug Event**			
	Accidental/ Unintentional	**Allergic Reaction**	**Adverse Effect**	**Total**
<2 years	13	1	0	14
2-5 years	19	4	3	26
6-11 years	4	6	1	11
12-18 years	4	13	5	22
Total	**40**	**24**	**9**	**73**
Codeine-containing Analgesic Products				
Age Group	**Adverse Drug Event**			
	Accidental/ Unintentional	**Allergic Reaction**	**Adverse Effect**	**Total**
<2 years	27	5	0	32
2-5 years	29	17	10	56
6-11 years	4	34	19	57
12-18 years	14	61	41	116
Total	**74**	**117**	**70**	**261**

Table 4.2.3.3 provides a summary description of the adverse effect that the physician determined was the cause of the ED visit. For ED visits involving cough and cold products, nine ED visits were the result of an adverse effect. Abdominal Pain/epigastric discomfort was the only adverse effect listed more than once (three visits).

For codeine-containing analgesic products, the majority of the adverse effects involved gastrointestinal issues. There were 79 ED cases related to gastro-intestinal complaints such as nausea, vomiting, epigastric discomfort or constipation. For ED visits related to difficulty breathing, there were 10 ED visits involving shortness of breath and nine cases involving chest pain, or difficulty breathing or other cardiac related symptoms. A more detailed table of the adverse effect descriptions can be found in Appendix L (Table L.1.).

Table 4.2.3.3 Summary Description and Frequency of Adverse Effects for Codeine-containing Pediatric ED Visits

Codeine-containing Cough and Cold ED Visits	
Manifestation	**Number of Events**
Gastro-Intestinal Complaints	3
Dizziness/syncope	2
Dyspnoea (difficult or labored breathing)	1
Dystonia (involuntary muscle contraction)	1
Somnolence	1
Visual Hallucination*	1
Total	**9**
Codeine-containing Analgesic ED Visits**	
Manifestation	**Number of Events**
Gastro-Intestinal Complaints	79
Dyspnoea (difficult or labored breathing)	10
Chest Pain/Tachycardia/abnormal heart rate	9
Dizziness/syncope	9
Altered/Depressed Level of Consciousness	8
Somnolence	4
Pruritus	2
Throat Tightness	2
Feeling Hot/Hyperhidrosis	2
Anorexia	1
Drug Intolerance	1
Headache	1
Laceration	1
Total	**129**

*other drugs were present, but codeine-containing substance still considered probable cause of event
**Since each ED visit could involve multiple manifestations, the total is greater than the number of cases.

In a previous review[30], DEPI identified 14 pediatric ED cases of children aged 2-18 years of age in the NEISS-CADES dataset for the years 2004-2010 that were the result of adverse reactions involving patients where the use of codeine products was indicated for pain from tonsillectomy. There were no new ED visits involving the use of codeine-containing products indicated for tonsillectomy pain found for years 2011-2013.

5 DISCUSSION

The drug utilization data showed declines in the OTC retail sales of cough/cold codeine-containing products to the consumers, and the number of pediatric patients (0-18 years) who received cough/cold and analgesic codeine-containing products from outpatient retail pharmacies, from 2010 through 2014. Despite the decrease, there remained a considerable number of pediatric patients who received

prescription codeine products with the largest proportion of these pediatric patients aged 0-11 years, and receiving **analgesic** codeine-containing products.

Based on U.S. office-based physician survey data, little to no use of analgesic codeine-containing products was reported in the pediatric age subgroups during the 2010-2014 period for conditions related to tonsillectomy and/or adenoidectomy. These diagnoses data were obtained from surveys completed by a sample of 3,200 office-based physicians reporting on patient activity during one day per month. Because of the small sample sizes with correspondingly large confidence intervals, the drug use mentions <100,000 are too low to provide reliable national estimates for the indications for use (diagnoses) and therefore, preclude meaningful interpretation of data trends. As a result, it is best to use the physician survey data only to gain insight on how drug products are prescribed in clinical practice, and to use the patient data from outpatient retail pharmacies to evaluate trends over time.

In FAERS data, this review identified 64 serious pediatric cases of respiratory depression with codeine-containing products over a 50-year period. A majority of the cases occurred in children less than 12 years of age. The most frequently reported codeine-containing product was acetaminophen with codeine. Consistent with this finding, approximately half of the 64 cases reported pain management as the reason for use. Promethazine with codeine (with and without phenylephrine) was the primary product involved in the cough and cold setting. A temporal relationship was observed, with the events occurring as early as after one dose of a codeine-containing product. Overall, it was difficult to determine if an appropriate codeine dose was administered in most cases, because of the paucity of information in the reports and changes in dosing recommendations over time.

Age appears to affect the outcome of the development of respiratory depression with codeine-containing product administration. Among the 24 deaths in the FAERS case series, 21 involved children less than 12 years old. In some cases, there may have been other factors that could have contributed to the death. The current label contraindicates use of codeine-containing products in children following tonsillectomy and/or adenoidectomy. Twelve of those 21 death cases reported use of a codeine-containing product for reasons other than pain management following tonsillectomy and/or adenoidectomy. Although it is unknown if this distribution is representative, it is interesting to note that among the 21 death cases with a known use, seven were for pain management following tonsillectomy and/or adenoidectomy, seven were for cough and cold, and five were for other pain use.

Regarding genotyping, only ten of 64 reports in this case series mentioned the status of CYP2D6 genotype: three were extensive metabolizers, with one death, and seven were ultra-rapid metabolizers with five deaths. It is unknown if these cases are representative. Also, it should be noted that there is a large amount of variability within patients who are genotyped as extensive metabolizers, and it is possible that some of these patients may develop symptoms similar to those of patients genotyped as ultra-rapid metabolizers.[31] Because of this variability in genotyping, it is unknown if genotyping can be used to reliably predict the risk of respiratory depression with codeine-containing products.

Medical conditions that cause respiratory compromise (such as pediatric obstructive sleep apnea) may increase the risk of respiratory depression.[32] Nine of the 24 deaths in the FAERS case series reported obstructive sleep apnea or enlarged tonsils; two of nine cases involved codeine-containing product use for reasons other than pain management following tonsillectomy and/or adenoidectomy.

It should be noted that FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

The review of literature case reports found an article that cited the death of three children after administration of codeine for management of postoperative pain or as a cough suppressant. All three children were overweight; however, the authors stated that the prescribed codeine doses were within the recommended dose range. One of the deceased children was found to be an extensive metabolizer. As discussed earlier, extensive metabolizers of CYP2D6 may develop symptoms similar to those of patients genotyped as ultra-rapid metabolizers.

For the DAWN ED data, the most important limitation is under ascertainment of events. Adverse drug events not severe enough to result in an ED visit, or events resulting in death before arrival at an ED, will not be captured in these data. There are also no data in DAWN on: a) whether the ED visit resulted from use of the drug that was prescribed to the patient or if it was the result of taking a medication via a friend or family member, or b) the reason the medication was used. The other limitation of examining ADR events is that it will include both allergic reactions as well as other adverse events that may be the result of underlying respiratory issues and/or possibly the result of ultra-rapid metabolism of codeine, but that information isn't collected in DAWN. Notwithstanding these limitations, modest-moderate national annual estimates of ED visits for ADRs for codeine-containing **analgesic** products were found in the U.S. pediatric population. The estimates had over-lapping confidence intervals for children in all three of the age-bands: 0-5 years of age, 6-11 years of age, and 12-18 years of age. Overall, there were roughly 500-1700 ED visits per year, for children <6 years old, 6-11 years old and 12-17 years old in the period from 2004 to 2011, with no significant increases or decreases between years. The lack of stable DAWN ED estimates related to codeine-containing **cough and cold** products may be attributable to lower pediatric utilization of codeine-containing cough and cold products compared to codeine-containing analgesic products.

Regarding the NEISS-CADES dataset, pediatric ED visits related to codeine-containing products are also likely to be under-ascertained for two reasons:

- only visits by patients alive at the time of discharge from the ED are included; and
- only visits for conditions that the treating clinician explicitly attributed to the use of a drug or a drug-specific effect are included.

In addition, the NEISS-CADES data do not provide enough details to determine if these adverse events were associated with the patient being a rapid metabolizer of codeine.

Notwithstanding these limitations, the NEISS-CADES data provide some evidence in the US of ED visits involving children and codeine-containing **cold/cough** products, specifically for codeine-promethazine and codeine-guaifenesin products The case numbers are modest[f], and in the under 6 year olds, the majority of the cases seem to be due to accidental/ unintentional ingestion. For pediatric ED visits involving **analgesic** products, there are higher case numbers in NEISS-CADES than for the cold/cough products. The most common analgesic codeine-containing products involved in the ED visits were acetaminophen/codeine combination products; accounting for >90% (246 of 261) of the codeine analgesic-related ED visits. The most common adverse events associated with analgesic codeine use that resulted in an ED visit in patients 0 to 18 years of age resulted from accidental exposures and allergic reactions, in the youngest age group (<2 years old), in particular. For ED visits categorized as due to an adverse effect, unfortunately, the data do not provide enough detail to determine if the patient was a rapid metabolizer of codeine.

The lack of new ED visits involving the use of codeine-containing products given for pain post tonsillectomy in the 2011-2013 NEISS-CADES data may be the result of under-ascertainment, but may also be the result of a change in prescribing of codeine products for the indication of pain for T/A.

6 CONCLUSIONS

Overall, OSE concludes that there are case reports of respiratory depression, sometimes resulting in death, following the use of codeine-containing products for both pain and cold/cough treatment, particularly in the pediatric population less than 12 years of age. Although a decrease in both OTC and pediatric prescription use of codeine-containing products was observed, 1.9 million pediatric patients received codeine-containing prescriptions from outpatient retail pharmacies in 2014. Although small in number, the FAERS cases of pediatric deaths with respiratory depression after codeine-containing product exposure occurred when the products were used not only for pain management following tonsillectomy and/or adenoidectomy, but also for other pain management and for cold/cough management. The FAERS, NEISS-CADES, and DAWN case data largely cannot be used to generate reliable national estimates, and the demonstrated levels of adverse effects and emergency department visits for children exposed to codeine products appear only modest-moderate. But there are respiratory depression cases following codeine-containing product use in pediatric patients in both the FAERS data and the NEISS-CADES emergency department visits data. We can't determine the true magnitude of the problem, but we also cannot conclude from these data that there is not a significant risk. We conclude that given the high pediatric use of these codeine products, these data do raise concern and interest in consideration of further regulatory action to promote safer use of codeine products in the pediatric population.

[f] There aren't enough cases to generate reliable national estimates.

7 APPENDICES

7.1 APPENDIX A: DRUG UTILIZATION DATABASE DESCRIPTIONS AND LIMITATIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

OTC International Market Tracking (OTCIMS)

The OTC International Market Tracking (OTCIMS) platform can provide the FDA with highly accurate retail sales data of non-prescription bound medicines, both registered and unregistered products. The USA data in the OTCIMS database represents scanned POS data, reporting on what the consumer purchased. The data represents the following channels: Food stores with Pharmacy, Drug and Mass Merchandiser excluding WalMart and Club Stores. Specialty stores, kiosks, internet sales, phone sales, etc. are not included. Data are represented in the OTC classification system (how the products are promoted to the consumers). All data are projected nationally. OTCIMS tracks key molecular data characteristics, strength of active ingredients; dosage form; and size of drug products by mL, number of tablets/ capsules, and/or total doses available. OTCIMS data is delivered quarterly in CD format and accessible through a secure, stand-alone desktop application called Dataview ™.

IMS Health, Vector One®: Total Patient Tracker (TPT)

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

IMS Health, National Prescription Audit

The National Prescription Audit (NPA™) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures both what is prescribed by the physician and what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies.

NPA™ receives over 2.7 billion prescription claims per year, captured from a sample of the universe of approximately 57,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 86% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 40 - 70% (varies by class and geography) of mail service pharmacies and approximately 45-55% of long-term care pharmacies. Data are available on-line for 72- rolling months with a lag of 1 month.

Encuity Research, LLC., TreatmentAnswers™ with Pain Panel

Encuity Research, LLC., TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Indications for use were obtained using a monthly survey of 3,200 office-based physicians. Although these data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, physician survey data are best used to identify the typical uses for the products in clinical practice, and the patient data from outpatient retail pharmacies to evaluate trends over time. Results should not be over emphasized when nationally projected estimates of annual uses or mentions fall below 100,000 as the sample size is very small with correspondingly large confidence intervals.

7.2 APPENDIX B: TABLES FOR DRUG UTILIZATION DATA

Table 2.3.1. National estimates of bottles/packages of *cough/cold* *codeine*-containing products sold over-the-counter to the consumers from U.S. retail store outlets, years 2010-2014

	Year									
	2010		2011		2012		2013		2014	
	Units*	%	Units*	%	Units*	%	Units*	%	Units*	%
Total Retail Sales of Cough/Cold Codeine-Containing Products	**1,165,094**	***100.0%***	**1,272,621**	***100.0%***	**678,730**	***100.0%***	**301,294**	***100.0%***	**169,300**	***100.0%***
Codeine-Guaifenesin	357,958	*30.7%*	413,832	*32.5%*	410,703	*60.5%*	301,036	*99.9%*	169,300	*100.0%*
Codeine-Dextromethorphan-Acetaminophen-Pseudoephedrine	806,986	*69.3%*	858,789	*67.5%*	268,027	*39.5%*	257	*0.1%*	--	--
Codeine-Acetaminophen-Phenylephrine	150	*<1%*	--	--	--	--	1	*<1%*	--	--

Source: IMS Health, OTC International Market Tracking. Years 2010-2014. Data extracted July 2015. Files: OTCIMS 2015-1124 total codeine class brand pack molecule 7-8-2015.dvf; OTCIMS 2015-1124 total codeine class brand pack molecule 2010 7-8-2015.dvf

*Units refer to the number of bottles/packages sold.

Table 2.3.2. National estimates of *patients* who received dispensed prescriptions for cough/cold and analgesic *codeine-containing* products, stratified by patient age*, drug class, and top 2 active ingredients, from U.S. outpatient retail pharmacies, years 2010-2014

	Year									
	2010		2011		2012		2013		2014	
	N	%	N	%	N	%	N	%	N	%
Total patients on *codeine-containing* products	**16,934,538**	***100.0%***	**17,238,831**	***100.0%***	**15,737,075**	***100.0%***	**15,334,314**	***100.0%***	**13,172,182**	***100.0%***
0 - 18 years	3,149,186	*18.6%*	2,915,932	*16.9%*	2,865,936	*18.2%*	2,549,097	*16.6%*	1,884,768	*14.3%*
0 - 11 years	1,814,435	*57.6%*	1,622,631	*55.6%*	1,716,250	*59.9%*	1,500,931	*58.9%*	1,051,339	*55.8%*
0 - 1 years	140,864	*7.8%*	114,867	*7.1%*	123,304	*7.2%*	97,092	*6.5%*	67,254	*6.4%*
2 - 5 years	665,900	*36.7%*	583,292	*35.9%*	616,474	*35.9%*	510,103	*34.0%*	331,202	*31.5%*
6 - 11 years	1,017,639	*56.1%*	933,076	*57.5%*	985,666	*57.4%*	901,334	*60.1%*	657,163	*62.5%*
12 - 18 years	1,339,544	*42.5%*	1,297,194	*44.5%*	1,155,565	*40.3%*	1,054,488	*41.4%*	838,135	*44.5%*
19+ years	13,736,354	*81.1%*	14,255,489	*82.7%*	12,900,588	*82.0%*	12,847,240	*83.8%*	11,307,084	*85.8%*
Unknown age	3,997	*<1%*	1,079	*<1%*	435	*<1%*	1,088	*<1%*	42,260	*0.3%*
Pediatric patients (*0-18 years*) on *codeine-containing* products	**3,149,186**	***100.0%***	**2,915,932**	***100.0%***	**2,865,936**	***100.0%***	**2,549,097**	***100.0%***	**1,884,768**	***100.0%***
Analgesic products	2,024,792	*64.3%*	1,810,545	*62.1%*	1,916,519	*66.9%*	1,720,497	*67.5%*	1,424,503	*75.6%*
0 - 11 years	1,178,727	*58.2%*	1,008,605	*55.7%*	1,200,098	*62.6%*	1,084,501	*63.0%*	847,264	*59.5%*
0 - 1 years	112,173	*9.5%*	89,571	*8.9%*	104,892	*8.7%*	84,192	*7.8%*	62,208	*7.3%*
2 - 5 years	422,926	*35.9%*	356,955	*35.4%*	431,341	*35.9%*	371,702	*34.3%*	271,110	*32.0%*
6 - 11 years	646,515	*54.8%*	564,444	*56.0%*	666,980	*55.6%*	631,429	*58.2%*	516,025	*60.9%*
12 - 18 years	847,357	*41.8%*	802,046	*44.3%*	721,091	*37.6%*	642,481	*37.3%*	581,528	*40.8%*
Cough/Cold combination products	1,180,132	*37.5%*	1,156,046	*39.6%*	998,166	*34.8%*	869,980	*34.1%*	482,629	*25.6%*
0 - 11 years	664,111	*56.3%*	637,477	*55.1%*	545,023	*54.6%*	442,654	*50.9%*	216,669	*44.9%*
0 - 1 years	29,550	*4.4%*	25,777	*4.0%*	19,350	*3.6%*	13,774	*3.1%*	5,444	*2.5%*
2 - 5 years	252,337	*38.0%*	233,384	*36.6%*	195,585	*35.9%*	147,687	*33.4%*	63,944	*29.5%*
6 - 11 years	387,732	*58.4%*	383,425	*60.1%*	334,223	*61.3%*	284,345	*64.2%*	148,599	*68.6%*
12 - 18 years	518,267	*43.9%*	520,768	*45.0%*	454,913	*45.6%*	428,929	*49.3%*	266,827	*55.3%*
Pediatric patients (*0-18 years*) on *codeine-containing* products	**3,149,186**	***100.0%***	**2,915,932**	***100.0%***	**2,865,936**	***100.0%***	**2,549,097**	***100.0%***	**1,884,768**	***100.0%***
Analgesic products	2,024,792	*64.3%*	1,810,545	*62.1%*	1,916,519	*66.9%*	1,720,497	*67.5%*	1,424,503	*75.6%*
Codeine-Acetaminophen	2,017,223	*99.6%*	1,803,387	*99.6%*	1,910,297	*99.7%*	1,714,662	*99.7%*	1,418,903	*99.6%*
Single-Ingredient codeine	3,236	*0.2%*	2,946	*0.2%*	2,723	*0.1%*	2,654	*0.2%*	2,817	*0.2%*
All others	4,749	*0.2%*	4,514	*0.2%*	4,300	*0.2%*	4,123	*0.2%*	3,652	*0.3%*
Cough/Cold combination products	1,180,132	*37.5%*	1,156,046	*39.6%*	998,166	*34.8%*	869,980	*34.1%*	482,629	*25.6%*
Codeine-Guaifenesin	691,993	*58.6%*	680,547	*58.9%*	629,152	*63.0%*	554,442	*63.7%*	249,786	*51.8%*
Codeine-Promethazine	402,926	*34.1%*	386,827	*33.5%*	306,089	*30.7%*	267,836	*30.8%*	201,814	*41.8%*
All others	106,575	*9.0%*	108,115	*9.4%*	79,191	*7.9%*	62,000	*7.1%*	37,081	*7.7%*

Source: IMS Health, Vector One®: Total Patient Tracker. Years 2010-2014. Data extracted June and August 2015. Files: TPT 2015-1124 total codeine age 6-29-2015.xls; TPT 2015-1124 codeine cough_cold combo 0-18 age molecule 6-29-2015.xls; TPT 2015-1124 codeine analgesics combo 0-18 age molecule 6-29-2015.xls

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0 - 16 years includes patients aged 16 years and 11 months.

**Summing patients across patient age bands and time periods will result in double counting and overestimates of patient counts. Moreover, the sum of the percentages will be greater than 100% because patients are double counted across age bands.

Table 2.3.3. National estimates of *prescriptions dispensed* for cough/cold and analgesic *codeine-containing* products, stratified by top 10 prescriber specialties, from U.S. outpatient retail pharmacies, cumulative years 2010-2014

	Cumulative 1/2010-12/2014	
	TRx	%
Total *prescriptions* dispensed for *codeine-containing* products	**125,584,453**	***100.0%***
Analgesic products	65,495,827	*52.2%*
Family Practice/General Practice/Doctor of Osteopathy	15,593,842	*23.8%*
Dentistry	12,425,953	*19.0%*
Internal Medicine	7,893,109	*12.1%*
Physician Assistant	3,441,923	*5.3%*
Emergency Medicine	3,116,249	*4.8%*
Nurse Practitioner	2,741,893	*4.2%*
Obstetrics and Gynecology	2,600,279	*4.0%*
Orthopedic Surgery	2,429,300	*3.7%*
Unspecified	2,411,281	*3.7%*
Otolaryngology	1,554,690	*2.4%*
All Others	11,287,308	*17.2%*

	Cumulative 1/2010-12/2014	
	TRx	%
Total *prescriptions* dispensed for *codeine-containing* products	**125,584,453**	***100.0%***
Cough/Cold products	60,088,626	*47.9%*
Family Practice/General Practice/Doctor of Osteopathy	25,901,298	*43.1%*
Internal Medicine	12,370,979	*20.6%*
Nurse Practitioner	5,651,973	*9.4%*
Physician Assistant	5,580,742	*9.3%*
Emergency Medicine	2,489,606	*4.1%*
Pediatrician	2,343,937	*3.9%*
Unspecified	1,335,709	*2.2%*
Pulmonary Disease	637,860	*1.1%*
Obstetrics and Gynecology	445,547	*0.7%*
Cardiology	397,672	*0.7%*
All Others	2,933,303	*4.9%*

Source: IMS Health, National Prescriptions Audit™. Years 2010-2014. Data extracted August 2015. File: NPA 2015-1124 total codeine TSI AC USC3 MD 8-18-2015.xlsx

Table 2.3.4. Top 5 diagnoses associated with the use of analgesic codeine-containing products, stratified by patient age, as reported from U.S. office-based physician surveys, years 2010 and 2014

	Year 2010			Year 2014		
	Uses	95% CI	%	Uses	95% CI	%
Total Codeine Uses	**11,983,000**	**11,467,000 - 12,500,000**	***100.0%***	**11,609,000**	**11,070,000 - 12,148,000**	***100.0%***
Analgesic products	6,513,000	6,132,000 - 6,894,000	*54.4%*	6,108,000	5,717,000 - 6,499,000	*52.6%*
0-18 years	1,341,000	1,168,000 - 1,514,000	*20.6%*	1,198,000	1,024,000 - 1,371,000	*19.6%*
0-1 years	73,000	32,000 - 113,000	*5.4%*	44,000	11,000 - 77,000	*3.7%*
7547 OTH CONG FOOT DEFORM	16,000	<500 - 35,000	*22.1%*	**8210 FX FEMUR SHAFT/NOS-CLOSE**	20,000	<500 - 43,000	*45.9%*
8350 DISLOCATION HIP-CLOSED	12,000	<500 - 28,000	*16.6%*	**9272 CRUSHING INJ WRIST/HAND**	18,000	<500 - 39,000	*40.9%*
7548 OTH NONTERATOGENIC ANOM	12,000	<500 - 28,000	*16.6%*	**0542 HERPETIC GINGIVOSTOMAT**	6,000	<500 - 18,000	*13.2%*
3829 OTITIS MEDIA NOS	10,000	<500 - 25,000	*14.0%*	**2-5 years**	201,000	130,000 - 272,000	*16.8%*
3814 NONSUPP OTITIS MEDIA NOS	7,000	<500 - 20,000	*10.1%*	**V670 SURGERY FOLLOW-UP**	52,000	16,000 - 88,000	*26.0%*
All Others	15,000	<500 - 33,000	*20.7%*	**9442 2ND DEGREE BURN HAND**	22,000	<500 - 45,000	*10.8%*
2-5 years	246,000	172,000 - 320,000	*18.3%*	**5531 UMBILICAL HERNIA**	21,000	<500 - 45,000	*10.7%*
3829 OTITIS MEDIA NOS	38,000	9,000 - 66,000	*15.3%*	**7556 OTH LOWER LIMB ANOMALIES**	19,000	<500 - 41,000	*9.7%*
5531 UMBILICAL HERNIA	35,000	7,000 - 62,000	*14.1%*	**8134 FX LOWER RADIUS/ULNA-CL**	18,000	<500 - 39,000	*9.0%*
5509 INGUINAL HERNIA NOS	16,000	<500 - 35,000	*6.6%*	**All Others**	68,000	27,000 - 109,000	*33.9%*
8138 FX RADIUS/ULNA NOS-CLOSE	15,000	<500 - 34,000	*6.2%*	**6-11 years**	370,000	274,000 - 467,000	*30.9%*
V670 SURGERY FOLLOW-UP	15,000	<500 - 33,000	*6.0%*	**8130 FX UPPER RADIUS/ULNA-CL**	55,000	18,000 - 92,000	*14.8%*
All Others	127,000	74,000 - 180,000	*51.8%*	**8100 FRACTURE CLAVICLE-CLOSED**	38,000	7,000 - 69,000	*10.3%*
6-11 years	430,000	333,000 - 528,000	*32.1%*	**8248 FX ANKLE NOS-CLOSED**	37,000	6,000 - 67,000	*9.9%*
8138 FX RADIUS/ULNA NOS-CLOSE	40,000	10,000 - 70,000	*9.3%*	**8140 FRACTURE CARPAL BONE-CL**	31,000	3,000 - 59,000	*8.4%*
8134 FX LOWER RADIUS/ULNA-CL	29,000	4,000 - 55,000	*6.8%*	**7468 CONG HEART ANOMALY NEC**	21,000	<500 - 43,000	*5.6%*
3829 OTITIS MEDIA NOS	29,000	4,000 - 54,000	*6.7%*	**All Others**	189,000	120,000 - 258,000	*51.0%*
5509 INGUINAL HERNIA NOS	27,000	2,000 - 51,000	*6.2%*	**12-18 years**	582,000	461,000 - 703,000	*48.6%*
V670 SURGERY FOLLOW-UP	22,000	<500 - 45,000	*5.2%*	**8134 FX LOWER RADIUS/ULNA-CL**	81,000	36,000 - 127,000	*14.0%*
All Others	283,000	204,000 - 363,000	*65.8%*	**V670 SURGERY FOLLOW-UP**	63,000	23,000 - 102,000	*10.8%*
12-18 years	593,000	478,000 - 708,000	*44.2%*	**8820 OPEN WOUND OF HAND**	36,000	6,000 - 66,000	*6.2%*
V670 SURGERY FOLLOW-UP	50,000	16,000 - 83,000	*8.4%*	**8150 FRACTURE METACARPAL-CLOS**	35,000	5,000 - 64,000	*6.0%*
8450 SPRAIN OF ANKLE	35,000	7,000 - 62,000	*5.8%*	**8160 FX PHALANGES, HAND-CLOSE**	35,000	5,000 - 64,000	*5.9%*
5509 INGUINAL HERNIA NOS	22,000	<500 - 44,000	*3.7%*	**All Others**	333,000	242,000 - 424,000	*57.2%*
8242 FX LATERAL MALLEOLUS-CL	21,000	<500 - 43,000	*3.6%*	**19+ years**	4,708,000	4,364,000 - 5,051,000	*77.1%*
8248 FX ANKLE NOS-CLOSED	19,000	<500 - 39,000	*3.2%*	**Unknown Age**	203,000	132,000 - 274,000	*3.3%*
All Others	447,000	347,000 - 547,000	*75.4%*				
19+ years	4,928,000	4,596,000 - 5,259,000	*75.7%*				
Unknown Age	244,000	170,000 - 317,000	*3.7%*				

Source: Encuity Research, LLC., TreatmentAnswers™. Years 2010 and 2014. Data extracted August 2015. Files: PDDA_2015-1124_total_codeine_2010_age_dx4_8-26-2015.xls; PDDA_2015-1124_total_codeine_2014_age_dx4_8-26-2015.xls

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0 - 16 years includes patients aged 16 years and 11 months.

Table 2.3.5. Top 5 diagnoses associated with the use of cough/cold codeine-containing products, stratified by patient age, as reported from U.S. office-based physician surveys, years 2010 and 2014

	Year 2010			Year 2014		
	Uses	95% CI	%	Uses	95% CI	%
Total Codeine Uses	**11,983,000**	**11,467,000 - 12,500,000**	***100.0%***	**11,609,000**	**11,070,000 - 12,148,000**	***100.0%***
Cough/Cold products	5,471,000	5,122,000 - 5,820,000	*45.7%*	5,501,000	5,129,000 - 5,872,000	*47.4%*
0-18 years	876,000	736,000 - 1,016,000	*16.0%*	581,000	460,000 - 702,000	*10.6%*
0-1 years	27,000	2,000 - 51,000	*3.1%*	10,000	<500 - 26,000	*1.7%*
4660 ACUTE BRONCHITIS	9,000	<500 - 23,000	*33.4%*	**4659 ACUTE URI NOS**	10,000	<500 - 26,000	*100.0%*
4659 ACUTE URI NOS	9,000	<500 - 23,000	*32.9%*	**2-5 years**	154,000	92,000 - 216,000	*26.5%*
4860 PNEUMONIA, ORGANISM NOS	5,000	<500 - 15,000	*17.3%*	**4659 ACUTE URI NOS**	113,000	59,000 - 166,000	*73.2%*
7862 COUGH	4,000	<500 - 14,000	*16.5%*	**4860 PNEUMONIA, ORGANISM NOS**	15,000	<500 - 34,000	*9.5%*
2-5 years	138,000	83,000 - 194,000	*15.8%*	**4939 ASTHMA NOS**	13,000	<500 - 30,000	*8.2%*
4659 ACUTE URI NOS	43,000	12,000 - 74,000	*31.3%*	**7862 COUGH**	8,000	<500 - 21,000	*4.9%*
7862 COUGH	33,000	6,000 - 60,000	*23.6%*	**4900 BRONCHITIS NOS**	6,000	<500 - 19,000	*4.2%*
4900 BRONCHITIS NOS	25,000	1,000 - 48,000	*17.9%*	**6-11 years**	104,000	53,000 - 156,000	*17.9%*
4644 CROUP	12,000	<500 - 29,000	*8.8%*	**4659 ACUTE URI NOS**	41,000	9,000 - 73,000	*39.2%*
3829 OTITIS MEDIA NOS	12,000	<500 - 28,000	*8.4%*	**7862 COUGH**	31,000	3,000 - 59,000	*29.7%*
All Others	14,000	<500 - 31,000	*10.0%*	**4810 PNEUMOCOCCAL PNEUMONIA**	9,000	<500 - 24,000	*8.6%*
6-11 years	335,000	248,000 - 421,000	*38.2%*	**4900 BRONCHITIS NOS**	9,000	<500 - 23,000	*8.3%*
7862 COUGH	78,000	36,000 - 120,000	*23.4%*	**4939 ASTHMA NOS**	8,000	<500 - 21,000	*7.2%*
4659 ACUTE URI NOS	73,000	33,000 - 114,000	*21.9%*	**All Others**	7,000	<500 - 21,000	*6.9%*
4900 BRONCHITIS NOS	51,000	17,000 - 84,000	*15.1%*	**12-18 years**	313,000	224,000 - 401,000	*53.9%*
4860 PNEUMONIA, ORGANISM NOS	28,000	3,000 - 52,000	*8.2%*	**4659 ACUTE URI NOS**	127,000	70,000 - 183,000	*40.5%*
3829 OTITIS MEDIA NOS	24,000	1,000 - 47,000	*7.1%*	**4900 BRONCHITIS NOS**	63,000	24,000 - 103,000	*20.3%*
All Others	81,000	39,000 - 124,000	*24.3%*	**7862 COUGH**	56,000	19,000 - 94,000	*17.9%*
12-18 years	376,000	285,000 - 468,000	*42.9%*	**4660 ACUTE BRONCHITIS**	25,000	<500 - 51,000	*8.1%*
4659 ACUTE URI NOS	157,000	98,000 - 216,000	*41.7%*	**4871 FLU W RESP MANIFEST NEC**	24,000	<500 - 48,000	*7.6%*
7862 COUGH	48,000	15,000 - 80,000	*12.6%*	**All Others**	18,000	<500 - 39,000	*5.6%*
4900 BRONCHITIS NOS	39,000	9,000 - 68,000	*10.3%*	**19+ years**	4,881,000	4,531,000 - 5,230,000	*88.7%*
4660 ACUTE BRONCHITIS	35,000	7,000 - 63,000	*9.3%*	**Unknown Age**	39,000	8,000 - 70,000	*0.7%*
4620 ACUTE PHARYNGITIS	28,000	3,000 - 53,000	*7.4%*				
All Others	70,000	30,000 - 109,000	*18.6%*				
19+ years	4,485,000	4,168,000 - 4,801,000	*82.0%*				
Unknown Age	110,000	61,000 - 160,000	*2.0%*				

Source: Encuity Research, LLC., TreatmentAnswers™. Years 2010 and 2014. Data extracted August 2015. Files: PDDA_2015-1124_total_codeine_2010_age_dx4_8-26-2015.xls; PDDA_2015-1124_total_codeine_2014_age_dx4_8-26-2015.xls

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0 - 16 years includes patients aged 16 years and 11 months.

7.3 APPENDIX C. WARNINGS, PRECAUTIONS, DOSING AND ADMINISTRATION AND ADVERSE REACTIONS LABELING FOR PROMETHAZINE WITH CODEINE

WARNINGS

Respiratory Depression in Children:

The combination of promethazine hydrochloride and codeine phosphate is contraindicated in pediatric patients less than 6 years of age. Concomitant administration of promethazine products with other respiratory depressants has an association with respiratory depression, and sometimes death, in pediatric patients.

Respiratory depression leading to arrest, coma, and death has occurred with the use of codeine antitussives in young children, particularly in the under-one-year infants whose ability to deactivate the drug is not fully developed.

Codeine

- Death Related to Ultra-Rapid Metabolism of Codeine to Morphine

Respiratory depression and death have occurred in children who received codeine in the post-operative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 [CYP2D6] or high morphine concentrations). Deaths have also occurred in nursing infants who were exposed to high levels of morphine in breast milk because their mothers were ultra-rapid metabolizers of codeine. (See **PRECAUTIONS-Nursing Mothers**).

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (gene duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing).

Children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine is contraindicated for post- operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy. (See **CONTRAINDICATIONS**).

When prescribing codeine-containing drugs, healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of morphine overdose.

• Dosage of codeine SHOULD NOT BE INCREASED if cough fails to respond; an unresponsive cough should be reevaluated in 5 days or sooner for possible underlying pathology, such as foreign body or lower respiratory tract disease.

• Codeine may cause or aggravate constipation.

• Administration of codeine may be accomplished by histamine release and should be used with caution in atopic children.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of narcotic analgesics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, intracranial lesions, or a preexisting increase in intracranial pressure. Narcotics may produce adverse reactions which may obscure the clinical course of patients with head injuries.

Asthma and other Respiratory Conditions: Narcotic analgesics or cough suppressants, including codeine, should not be used in asthmatic patients (see Contraindications). Nor should they be used in acute febrile illness associated with productive cough or in chronic respiratory disease where interference with ability to clear the tracheobronchial tree of secretions would have a deleterious effect on the patient's respiratory function

Hypotensive Effect: Codeine may produce orthostatic hypotension in ambulatory patients.

PRECAUTIONS

Nursing Mothers: Nursing mothers taking codeine can have higher morphine levels in their breast milk if they are ultra-rapid metabolizers. These higher levels of morphine in breast milk may lead to life-threatening or fatal side effects in nursing babies.

Information for Patients:

Advise patients that some people have a genetic variation that results in codeine changing into morphine more rapidly and completely than other people. Most people are unaware of whether they are an ultra-rapid codeine metabolizer or not. These higher-than-normal levels of morphine in the blood may lead to life-threatening or fatal respiratory depression or signs of overdose such as extreme sleepiness, confusion, or shallow breathing. Children with this genetic variation who were prescribed codeine after tonsillectomy and/or adenoidectomy for obstructive sleep apnea may be at greatest risk based on reports of several deaths in this population due to respiratory depression. As a result, codeine is contraindicated in children who undergo tonsillectomy and/or adenoidectomy. Advise caregivers of children receiving codeine for other reasons to monitor for signs of respiratory depression.

Patients should be advised to measure Promethazine HCl, Phenylephrine HCl and Codeine Phosphate Oral Solution with an accurate measuring device. A household teaspoon is not an accurate measuring device and could lead to overdosage, especially when a half a teaspoon is measured. A pharmacist can recommend an appropriate measuring device and can provide instructions for measuring the correct dose.

DOSING AND ADMINISTRATION

Promethazine with codeine syrup contains promethazine hydrochloride 6.25mg/5ml, codeine phosphate 10mg/5ml and alcohol 7 percent. It is important that Promethazine HCl and Codeine Phosphate Oral Solution is measured with an accurate measuring device (see **PRECAUTIONS-Information for Patients**). A household teaspoon is not an accurate measuring device and could lead to overdosage, especially when half a teaspoon is to be measured. It is strongly recommended that an accurate measuring device be used. A pharmacist can provide an appropriate device and can provide instructions for measuring the correct dose.

The combination of promethazine hydrochloride and codeine phosphate is contraindicated in pediatric patients less than 6 years of age, because the combination may cause fatal respiratory depression in this age population.

The average effective dose is given in the following table:

Adults (12 years of age and over)	5 mL (1 teaspoonful) every 4 to 6 hours, not to exceed 30 mL in 24 hours.
Children 6 years to under 12 years	2.5 mL to 5 mL (½ to 1 teaspoonful) every 4 to 6 hours, not to exceed 30mL in 24 hours.

ADVERSE REACTIONS
Central Nervous System: *CNS depression, particularly respiratory depression, and to a lesser extent circulatory depression; light-headedness, dizziness, sedation, euphoria, dysphoria, headache, transient hallucination, disorientation, visual disturbances, and convulsions.*

Cardiovascular: *Tachycardia, bradycardia, palpitation, faintness, syncope, orthostatic hypotension (common to narcotic analgesics).*

Gastrointestinal: *Nausea, vomiting, constipation, and biliary tract spasm. Patients with chronic ulcerative colitis may experience increased colonic motility; in patients with acute ulcerative colitis, toxic dilation has been reported.*

Genitourinary: *Oliguria, urinary retention, antidiuretic effect has been reported (common to narcotic analgesics).*

Allergic*: Infrequent pruritus, giant urticaria, angioneurotic edema, and laryngeal edema.*

Other: *Flushing of the face, sweating and pruritus (due to opiate-induced histamine release); weakness.*

7.4 APPENDIX D. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

7.5 APPENDIX E. LIST OF PREFERRED TERMS ASSOCIATED WITH HIGH LEVEL TERMS USED FOR RESPIRATORY DEPRESSION FAERS SEARCH

HLT	PT
Breathing abnormalities	Acute promyelocytic leukaemia differentiation syndrome, Apnoea, Apnoeic attack, Bradypnoea, Breath holding, Breathing-related sleep disorder, Cardiac asthma, Cardio-respiratory arrest, Central-alveolar hypoventilation, Cheyne-Stokes respiration, Congenital central hypoventilation syndrome, Dyspnoea, Dyspnoea at rest, Dyspnoea exertional, Dyspnoea paroxysmal nocturnal, Grunting, Hyperventilation, Hypopnoea, Hypoventilation, Kussmaul respiration, Mouth breathing, Nocturnal dyspnoea, Orthopnoea, Pickwickian syndrome, Platypnoea, Prolonged expiration, Psychogenic respiratory distress, Respiratory arrest, Respiratory depression, Respiratory depth decreased, Respiratory depth increased, Respiratory distress, Respiratory dyskinesia, Retinoic acid syndrome, Sleep apnoea syndrome, Tachypnoea, Transfusion-associated dyspnoea, Trepopnoea, Upper airway resistance syndrome
Respiratory failures (excl. neonatal)	Acute respiratory failure, Cardiopulmonary failure, Cardio-respiratory distress, Chronic respiratory failure, Postoperative respiratory distress, Postoperative respiratory failure, Respiratory failure, Respiratory paralysis
Death and sudden death	Accidental death, Agonal death struggle, Brain death, Cardiac death, Completed suicide, Death, Death neonatal, Decapitation, Drowning, Electrocution, Euthanasia, Foetal death, Maternal death affecting foetus, Maternal death during childbirth, Stillbirth, Sudden cardiac death, Sudden death, Sudden infant death syndrome, Sudden unexplained death in epilepsy
Tracheal therapeutic procedures	Endotracheal intubation, Mini-tracheostomy, Tracheal fistula repair, Tracheal lesion excision, Tracheal operation, Tracheal plastic repair, Tracheobronchial stent insertion, Tracheobronchial stent removal, Tracheo-oesophageal puncture, Tracheostomy, Tracheostomy closure, Tracheostomy tube removal
Disturbances in consciousness NEC	Adams-Stokes syndrome, Altered state of consciousness, Apallic syndrome, Consciousness fluctuating, Delayed recovery from anaesthesia, Depressed level of consciousness, Gasping syndrome, Hyperglycaemic unconsciousness, Hyperosmolar hyperglycaemic state, Hypoglycaemic unconsciousness, Lethargy, Loss of consciousness, Neonatal oversedation, Postictal state, Post-injection delirium sedation syndrome, Preictal state, Psychogenic pseudosyncope, Sedation, Somnolence, Somnolence neonatal, Sopor, Stupor, Syncope
Coma states	Coma, Coma acidotic, Coma blister, Coma hepatic, Coma neonatal, Coma uraemic, Diabetic coma, Diabetic hyperglycaemic coma, Diabetic hyperosmolar coma, Diabetic ketoacidotic hyperglycaemic coma, Hypercapnic coma, Hypoglycaemic coma, Hyponatraemic coma, Myxoedema coma, Traumatic coma

HLT	PT
Conditions associated with abnormal gas exchange	Alveolar aeration excessive, Anaemic hypoxia, Anoxia, Asphyxia, Brain hypoxia, Cyanosis, Cyanosis central, Hypercapnia, Hypercapnic coma, Hyperoxia, Hypocapnia, Hypoxia, Hypoxic-ischaemic encephalopathy, Respiratory acidosis, Respiratory alkalosis, Respiratory gas exchange disorder

7.6 APPENDIX F. CHARACTERISTICS TABLE OF SEROUS PEDIATRIC FAERS CASES OF RESPIRATORY DEPRESSION REPORTED WITH CODEINE-CONTAINING PRODUCTS IN THE COUGH AND COLD AND ANALGESIC SETTINGS

Table 4. Descriptive characteristics of serious pediatric FAERS cases of respiratory depression reported with codeine-containing products in the cough and cold setting received by FDA as of May 26, 2015

(N = 14)

Sex	Male	8
	Female	6
Age (years)	Mean	2.7
	Median	2.2
	Range	12 days – 6
	0-1 year	6
	2-5 years	7
	6-11 years	1
	12-18 years	0
Country	United States	11
	Foreign	3
Initial FDA Received Year†	1975-2012	12
	2013	1
	2015	1
Event Year†	1975-2006	7
	2014	1
	Unknown	6
Report Type	Expedited	8
	Direct	4
	Periodic	2
Codeine-Containing Products	Promethazine, phenylephrine with codeine	4
	Codeine unspecified	3
	Promethazine with codeine	3
	Guaifenesin with codeine	2
	Chlorpheniramine, phenylephrine with dihydrocodeine	1
	Triprolidine, pseudoephedrine with codeine	1
Serious Outcomes*	Death	7
	Hospitalization	7
	Life-threatening	2
	Disability	1
	Other Serious	5

* Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important

Table 4. Descriptive characteristics of serious pediatric FAERS cases of respiratory depression reported with codeine-containing products in the cough and cold setting received by FDA as of May 26, 2015

(N = 14)

medical events. Reports may include multiple outcomes.

† Reports received prior to the DSC issued by the FDA in 2012 were grouped together.

Table 5. Descriptive characteristics of serious pediatric FAERS cases of respiratory depression reported with codeine-containing products in the analgesic setting received by FDA as of May 26, 2015

(N = 34)

Sex	Male	21
	Female	10
	Unknown	3
Age (years)	Mean	7.2
	Range	9 months – 17
	Median	5.5
	0-1 year	3
	2-5 years	13
	6-11 years	10
	12-18 years	8
Country	United States	20
	Foreign	14
Initial FDA Received Year†	1989-2012	20
	2013	8
	2014	6
Event Year†	1987-2012	15
	2013	3
	Unknown	16
Report Type	Expedited	23
	Direct	10
	Periodic	1
Codeine-Containing Products††	Acetaminophen with codeine	21
	Codeine unspecified	13
	Promethazine with codeine	1
Serious outcomes*	Death	14
	Hospitalization	10
	Life-threatening	13
	Disability	1
	Other Serious	15

* Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. Reports may include multiple outcomes.

† Reports received prior to the DSC issued by the FDA in 2012 were grouped together.

†† Cases may contain more than one codeine-containing product.

7.7 APPENDIX G. ADDITIONAL SAMPLE CASE NARRATIVES

Sample Respiratory Depression Case for Post Adenoidectomy and/or Tonsillectomy

FAERS Case # 9165725, Direct, US, Hospitalization, 2013: An 8-year-old female experienced respiratory problems after receiving acetaminophen with codeine liquid every 4 hours for pain after tonsillectomy/adenoidectomy, bilateral myringotomy, sinus surgery, and nasal reconstruction. The patient's respiratory problems persisted and continued to worsen for 18 hours requiring treatment with 2 doses of naloxone. The case report notes that the patient responded to the first dose of naloxone; however, no further detail was provided. The patient's past medical history included obstructive sleep apnea, reactive airway disease, eczema, chronic sinusitis, and chronic mastoiditis. The patient's mother further stated that "the acetaminophen with codeine liquid rapidly metabolized in her liver converting to morphine and overdosing our daughter."

Reviewer comment: The case report is from the patient's mother and is deficient in clinical details; however, it appears that the patient may have been an ultra-rapid metabolizer. This case was received in FAERS prior to the posting of the DSC and labeling update contraindicating the use of codeine for pain management following tonsillectomy and/or adenoidectomy (event date reported was February 2012).

Sample Respiratory Depression Case for Sore Throat/Tonsillitis

FAERS Case # 7272513, US, Death, 2010: A 5-year-old female was hospitalized for two days for rehydration due to an upper respiratory tract infection. During her hospital stay, she received oral sulfamethoxazole and trimethoprim, IV cefuroxime, and promethazine with codeine. After her discharge, she was prescribed acetaminophen with codeine elixir (1/2-1 teaspoonful every 4 hours for 3 days) for pain associated with a sore throat. Two days later, the child became very weak. She experienced respiratory and cardiac arrest while she was being transported to the doctor's office. The child was pronounced brain dead in the emergency department. Postmortem toxicology was "high for oxycodone;" however, oxycodone was never prescribed for this patient, which was verified by the parents and hospital. Other pertinent medical history included cerebral palsy, bladder infection, and recent upper respiratory tract infection. The cause of death was reported as cerebral palsy.

Reviewer comment: The patient received two different codeine-containing products over the course of several days and the cumulative depressant effect of both products may have contributed to the respiratory status of this patient. Because of the conflicting information reported regarding the administration of oxycodone, it is difficult to determine if codeine or oxycodone played a role in the death of this patient.

Sample Respiratory Depression Case for Unknown Use

FAERS Case # 10078290, Foreign, Hospitalization 2014: A 16-year-old male experienced respiratory depression following the administration of an unknown codeine product. The total dose was reported to be 110mg of unspecified codeine. He was treated with a naloxone infusion and recovered. Other concomitant medications included flucloxacillin, cefotaxime, clonazepam, and valproate.

Reviewer comment: This foreign case report lacked detailed information; however, it appeared that the patient experienced severe respiratory failure and required medical intervention with naloxone. It cannot be determined if the 110mg total codeine dose was appropriate for this patient, because the patient's weight was not reported and the frequency of administration was unknown. The patient was also receiving clonazepam,

which is labeled for respiratory depression and may have played a synergistic role in the patient's clinical course.

7.8 APPENDIX H. PEDIATRIC REPORTS OF RESPIRATORY DISTRESS WITH CODEINE-CONTAINING PRODUCTS WITH A SERIOUS OUTCOME[g]

7.8.1 *Case Definition*

Case Inclusion Criteria

- A temporal association following a codeine-containing product administration

AND

- Signs and symptoms consistent with acute respiratory distress, such as restlessness, anxiety, combativeness, somnolence, lethargy, tachypnea, abnormal airway sounds, stridor, wheezing, decreased respiratory rate, pallor, or cyanosis[h]

7.8.2 *FAERS Search Strategy*

Table 6. FAERS Search Strategy for Pediatric Reports with Codeine-containing Products with a Serious Outcome*	
Date of search	May 26, 2015
Time period of search	January 1, 1965 – May 26, 2015
Search type	FBIS quick query
Outcome	Serious[†]
Product terms	Product active ingredient: acetaminophen/codeine phosphate, acetyldihydrocodeine hydrochloride, codeine, codeine hydrochloride, codeine phosphate, codeine phosphate anhydrous, codeine polistirex, codeine sulfate, dihydrocodeine, dihydrocodeine bitartrate, dihydrocodeine phosphate
Age range	18 years of age and below
* See Appendix D for a description of the FAERS database. [†] Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. Reports may include multiple outcomes.	

We evaluated the reports that were retrieved from the search strategy in Table 6 and selected any PTs that suggest respiratory distress to identify potential reports (in Table 7 below).

Table 7. FAERS Search Strategy for Pediatric Reports of Respiratory Distress with Codeine-containing Products with a Serious Outcome*	
Date of search	May 26, 2015
Time period of search	January 1, 1965 – May 26, 2015
Search type	FBIS profile report
Outcome	Serious[†]
Product terms	Product active ingredient: acetaminophen/codeine phosphate, acetyldihydrocodeine hydrochloride, codeine,

[g] Reports contained within Appendices H, I and J may contain duplicates due to overlapping preferred terms within the search strategy that may have been reported within one report.

[h] Weiner DL. Emergency evaluation and immediate management of acute respiratory distress in children. In: UpToDate, Fleisher GR (Ed), UpToDate, Waltham, MA. (Accessed on June, 11 2015)

Table 7. FAERS Search Strategy for Pediatric Reports of Respiratory Distress with Codeine-containing Products with a Serious Outcome*	
	codeine hydrochloride, codeine phosphate, codeine phosphate anhydrous, codeine polistirex, codeine sulfate, dihydrocodeine, dihydrocodeine bitartrate, dihydrocodeine phosphate
MedDRA search terms (Version 18.0)	Preferred Terms (PTs): abasia, abnormal behavior, accidental exposure to product, accidental overdose, aggression, agitation, altered state of consciousness, amnesia, analgesic drug level above therapeutic, analgesic drug level increased, aphasia, blood pressure decreased, bronchopneumonia, cardiac arrest, circulatory collapse, confusional state, decreased activity, delirium, depression, disturbance in attention, dizziness, drug administration error, drug dispensing error, drug level above therapeutic, drug level increased, dysphagia, encephalopathy, feeling abnormal, feeling jittery, hallucination, hypersomnia, hypotension, hypotonia, incorrect dose administered, irritability, malaise, medication error, miosis, nervous system disorder, overdose, oxygen saturation decreased, pneumonia aspiration, presyncope, psychotic disorder, pupil fixed, respiratory disorder, respiratory rate decreased, seizure, skin discolouration, speech disorder, toxicity to various agents, unresponsive to stimuli, use of accessory respiratory muscles, and wheezing
Age range	18 years of age and below
* See Appendix D for a description of the FAERS database. † Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. Reports may include multiple outcomes.	

7.8.3 *Results*

This section summarizes the pediatric respiratory distress reports in aggregate. These summaries use crude counts of reports and may contain duplicate reports. A full analysis of the potential relationships between codeine-containing products and the adverse events reported in the individual reports was not conducted.

The FAERS search retrieved 627 pediatric reports with codeine-containing products with a serious outcome based on the search strategy described in Section 7.8.2, Table 6. We evaluated the reports that were retrieved from this search and selected any PTs that suggest respiratory distress to identify potential reports. The FAERS search (in Section 7.8.2, Table 7) retrieved 150 pediatric reports of respiratory distress with codeine-containing products with a serious outcome.
These 150 reports can be categorized as the following:

- Overdose – either from single substance (primary product was acetaminophen with codeine) or polysubstance abuse (such as combinations with opioids, benzodiazepines, and antidepressants); 37 reports had a death outcome
- Suicide attempts- no temporal association between codeine administration and the reported suicide attempt; codeine containing-product was ingested in combination with other substances
- Transplacental exposure
- Abnormal behavior – such as hallucinations and delirium primarily associated with influenza, promethazine or in combination with other opioids or antipsychotics
- Medication error – 2 reports had a death outcome: 1 duplicate report; see below for sample narrative

- Accidental ingestion – 2 reports had a death outcome: 1 duplicate report; 1 report from the American Association of Poison Control Centers regarding an instance of fatal drug intoxication with polysubstance ingestion in an 18-month old female
- Pain management – associated with post-surgery, post-tonsillectomy/adenoidectomy and pain due to cancer; 4 reports had a death outcome: 1 duplicate report, 1 report previously discussed in respiratory depression section, 1 death reported with hepatic failure secondary to acetaminophen toxicity, and 1 report discussed below
- Cough and cold use – 1 report had a death outcome; see below for sample narrative
- Miscoded age or suspect product

Reviewer comment: Most reports involved overdose related to polysubstance abuse or abnormal behavior (such as hallucinations and delirium) associated with influenza, promethazine or in combination with antipsychotics or other opioids. In children under the age of 12, there was one reported death involving codeine use for cough and cold and one involving pain management following tonsillectomy and/or adenoidectomy.

Sample narratives of death reports in patients < 12 years old

These cases met the case definition of respiratory depression, but were categorized under respiratory distress based on the search strategy.

FAERS Case # 13441470, US, Death, 1999: This is a literature case[i] involving a 29-day-old premature male who received 2 doses of 1ml of dihydrocodeine, chlorpheniramine and phenylephrine syrup (Novahistine DH) (0.63mg/kg of codeine) every 6 hours for cough and an upper respiratory infection and experienced opiate intoxication two hours after his last dose. The mother reported that the child was not breathing. The patient died despite life-saving measures. The cause of death upon autopsy was acute opiate intoxication with contributory findings of severe bronchitis/bronchiolitis. The authors commented that the premature infant was susceptible to drug intoxication as a result of an immature enzyme system. They additionally recommended that caution is advised when underlying respiratory conditions exist because these may compound the effects of opiates and contribute to respiratory depression.

Reviewer comment: The narrative suggests that the patient had respiratory depression. The current labeling for codeine-containing cough and cold products does not recommend use in children under the age of 6.

FAERS Case # 3218251, US, Death, 1999: A 5-year-old female received acetaminophen with codeine (1 teaspoon every 4 hours) for pain after tonsillectomy/adenoidectomy surgery and died 46 hours later. There were no complications with the surgery; however, she was noted to be very lethargic after the surgery. Autopsy results reported high blood levels of codeine, morphine, and acetaminophen. Her pertinent medical history included Smith-Magenis Syndrome. Concomitant medications for this patient included sevoflurane and midazolam (during surgery), melatonin, and valproic acid.

Reviewer comment: This case was received in FAERS prior to the posting of the DSC and labeling update contraindicating the use of codeine pain management following tonsillectomy and/or adenoidectomy.

FAERS Case # 4916370, US, Death, 1992: A 17-month-old male died after he was hospitalized for an ear, nose and throat procedure and was discharged with a prescription for acetaminophen with codeine #3 (1 to 1&1/2 teaspoons every 4 hours as needed for pain). The pharmacist called the physician for clarification of the

[i] Magnani B, Evans R. Codeine intoxication in the neonate. Pediatrics, December 1999; 104(6): e75.

prescription and subsequently added an additional 18mg of codeine to the already present 12mg of codeine per 5ml of acetaminophen with codeine elixir. This resulted in 30-45mg of codeine per dose. The patient died within 12 hours of receiving the first dose.

Reviewer comment: The current labeling for acetaminophen with codeine elixir does not have a contraindication based on age.

7.9 APPENDIX I. PEDIATRIC REPORTS OF DESIGNATED MEDICAL EVENTS (DME) WITH CODEINE-CONTAINING PRODUCTS WITH A SERIOUS OUTCOME[j]

Designated Medical Events are adverse events that are considered rare, serious, and associated with a high drug-attributable risk and which constitute an alarm with as few as one to three reports. The DME list is an internal tool used by reviewers in the Division of Pharmacovigilance and does not have any regulatory significance.

7.9.1 *Case Definition*

Case Inclusion Criteria

- All cases with Preferred Terms (PT) in the OSE Designated Medical Event list (see Appendix I, Section 7.9.4 for the list of events)

For the purpose of this review, as part of the designated medical events, we also included cases with the following PTs that describe suicidality: Intentional self-injury, Intentional overdose, Suicidal ideation, and Suicide attempt

7.9.2 *FAERS Search Strategy*

Table 8. FAERS Search Strategy for Pediatric Reports of Designated Medical Event (DME) with Codeine-containing Products with a Serious Outcome*	
Date of search	May 26, 2015
Time period of search	January 1, 1965 – May 26, 2015
Search type	FBIS profile report
Outcome	Serious[†]
Product terms	Product active ingredient: acetaminophen/codeine phosphate, acetyldihydrocodeine hydrochloride, codeine, codeine hydrochloride, codeine phosphate, codeine phosphate anhydrous, codeine polistirex, codeine sulfate, dihydrocodeine, dihydrocodeine bitartrate, dihydrocodeine phosphate
MedDRA search terms (Version 18.0)	OSE DME list: Acute pancreatitis, Acute respiratory failure, Agranulocytosis, Anaphylaxis and anaphylactoid reactions, Aplastic anemia, Blind, Congenital anomalies, Deaf, Disseminated intravascular coagulation, Endotoxic shock, confirmed or suspected, Hemolytic anemia, Haemolysis, Liver failure, Liver necrosis, Liver transplant, Pancytopenia, Pulmonary fibrosis, Pulmonary hypertension, Renal failure, Rhabdomyolysis, Seizure, Stevens-Johnson syndrome, Sudden death, Torsade de

[j] Reports contained within Appendices H, I and J may contain duplicates due to overlapping preferred terms within the search strategy that may have been reported within one report.

Table 8. FAERS Search Strategy for Pediatric Reports of Designated Medical Event (DME) with Codeine-containing Products with a Serious Outcome*	
	Pointes, Toxic epidermal necrolysis, Thrombotic thrombocytic purpura, Ventricular fibrillation, Suicide, Neuroleptic malignant syndrome, Amyotropic lateral sclerosis, Serotonin syndrome, Colitis ischaemic, Progressive multifocal leukoencephalopathy, Product infectious disease transmission†† Additional suicidality-related Preferred Terms (PTs): Intentional self-injury, Intentional overdose, Suicidal ideation, Suicide attempt
Age range	18 years of age and below
* See Appendix D for a description of the FAERS database. † Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. Reports may include multiple outcomes. †† See Appendix I, Section 7.9.4 for a description of PTs listed under each DME.	

7.9.3 ***Results***

This section summarizes designated medical events of interest in aggregate. These summaries use crude counts of reports and may contain duplicate reports. A full analysis of the potential relationships between codeine-containing products and the adverse events reported in the individual reports was not conducted.

The FAERS search retrieved 174 pediatric reports with codeine-containing products with a serious outcome based on the search strategy described in Table 4.

Among the 174 reports, the reports that were not summarized within the respiratory depression and respiratory distress sections can be categorized as the following:

- Suicidality – 48 reports had a death outcome
- Sudden death – associated with cardiac arrhythmia and cardio-respiratory arrest; 5 reports: 2 duplicate reports, 1 report had no mention of codeine use, 2 reports are discussed below
- Hepatic failure – related to frequent acetaminophen with codeine usage; 4 reports had a death outcome
- Pain management – associated with combination with other narcotics for cancer pain; 2 reports had a death outcome: 1 report was related to cancer and 1 report is discussed below
- Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis – all were associated with concomitant medications (such as antibiotics, non-steroidal anti-inflammatories and acetaminophen); 2 reports had a death outcome: 1 duplicate report
- Serotonin Syndrome – reports related to ziprasidone use; 1 report had a death outcome (this report was miscoded for death, outcome was noted as improved in the narrative)
- Overdose – related to polysubstance abuse; 1 report had a death outcome
- Miscoded suspect product

Reviewer comment: There were 2 sudden deaths reported in 2 children under the age of 12; both reports were coincident with codeine administration and were captured within the respiratory depression case series. Based on the remaining aggregate data, there were no new safety signals to note.

Sample narrative of reports of sudden death in patients < 12 years old

FAERS Case # 10661358, Foreign, Death, 2014: A 5-year-old male experienced cardio-respiratory arrest and died 7 hours after taking "doses of" amoxicillin (600mg), salbutamol, and 1 teaspoon of codeine phosphate hemihydrate for cold and cough. Other concomitant medications included valproic acid (600mg), clobazepam, and paliperidone. His pertinent medical history includes mental handicap, encephalopathy, epilepsy, and behavioral disorder.

Reviewer comment: This case was captured in the respiratory depression case series. This is a death case associated with codeine administration in a setting that is not mentioned in the current codeine labeling.

FAERS Case # 6516302, Foreign, Death, 2010: A 2-year-old male (estimated weight 15kg) with oral aphthae received codeine 15mg for pain and was found dead 5 hours after his third dose of codeine. Toxicology results revealed plasma levels of free form codeine to be 1,678mg/L (therapeutic range: 10-200mg/L, toxic range 30-500mg/L and lethal dose: above 1,600mg/L) and plasma levels of free form morphine to be 339mg/L. Cause of death was reported as "unexplained sudden death." He was also receiving valproate concomitantly for convulsions.

Reviewer comment: This case was captured in the respiratory depression case series. This is a death case associated with codeine administration in a setting that is not mentioned in the current codeine labeling.

7.9.4 *List of OSE Designated Medical Events and associated MedDRA Preferred Terms*

Designated Medical Event	**MedDRA Preferred Terms (Version 18.0 – updated May 4, 2015)**
Acute pancreatitis	Pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising, Pancreatic necrosis, Haemorrhagic necrotic pancreatitis
Acute respiratory failure	Acute respiratory failure, Respiratory failure, Acute respiratory distress syndrome
Agranulocytosis	Agranulocytosis, Neutropenia, Febrile neutropenia
Anaphylaxis and anaphylactoid reactions	Anaphylactic reaction, Anaphylactoid reaction, Anaphylactic shock, Anaphylactoid shock
Aplastic anemia	Aplastic anaemia, Bone marrow failure, Aplasia pure red cell
Blind	Blindness, Blindness transient, Blindness unilateral, Optic ischaemic neuropathy, Sudden visual loss
Congenital anomalies	Congenital anomaly
Deaf	Deafness, Deafness neurosensory, Deafness permanent, Deafness transitory, Deafness bilateral, Deafness unilateral, Sudden hearing loss
Disseminated intravascular coagulation	Disseminated intravascular coagulation
Endotoxic shock, confirmed or suspected	Endotoxic shock, Septic shock
Hemolytic anemia	Haemolytic anaemia, Coombs positive haemolytic anaemia, Coombs negative haemolytic anaemia
Haemolysis	Haemolysis, Intravascular haemolysis, Haemoglobinaemia, Haemoglobinuria, Haptoglobin decreased
Liver failure	Hepatic failure, Hepatic encephalopathy, Acute hepatic failure, Subacute hepatic failure
Liver necrosis	Hepatic necrosis, Hepatitis fulminant, Hepatitis acute
Liver transplant	Liver transplant
Pancytopenia	Pancytopenia
Pulmonary fibrosis	Pulmonary fibrosis

Designated Medical Event	MedDRA Preferred Terms (Version 18.0 – updated May 4, 2015)
Pulmonary hypertension	Pulmonary hypertension, Cor pulmonale
Renal failure	Acute kidney injury, Renal failure, Renal impairment
Rhabdomyolysis	Rhabdomyolysis
Seizure	Seizure, Epilepsy, Generalised tonic-clonic seizure
Stevens-Johnson syndrome	Stevens-Johnson syndrome, Erythema multiforme
Sudden death	Sudden death, Sudden cardiac death
Torsade de Pointes	Torsade de pointes
Toxic epidemal necrolysis	Toxic epidermal necrolysis, Dermatitis exfoliative
TTP	Thrombotic thrombocytopenic purpura
Ventricular fibrillation	Ventricular fibrillation
Suicide	Completed suicide
Neuroleptic malignant syndrome	Neuroleptic malignant syndrome
ALS - Amyotrophic lateral sclerosis	Amyotrophic lateral sclerosis
Serotonin syndrome	Serotonin syndrome
Colitis ischaemic	Colitis ischaemic, Intestinal infarction
PML - Progressive multifocal leukoencephalopathy	Progressive multifocal leukoencephalopathy
Product infectious disease transmission	Suspected transmission of an infectious agent via product, Transmission of an infectious agent via product, Product contamination microbial

7.10 APPENDIX J. PEDIATRIC REPORTS OF SUBSTANCE ABUSE WITH CODEINE-CONTAINING PRODUCTS WITH A SERIOUS OUTCOME[k]

7.10.1 *Case Definition*

Case Inclusion Criteria

- All cases within Standardised MedDRA Queries (SMQ) *Drug abuse and dependence*

7.10.2 *FAERS Search Strategy*

Table 9. FAERS Search Strategy for Pediatric Reports of Substance Abuse with Codeine-containing Products with a Serious Outcome*	
Date of search	May 26, 2015
Time period of search	January 1, 1965 – May 26, 2015
Search type	FBIS profile report
Outcome	Serious[†]
Product terms	Product active ingredient: acetaminophen/codeine phosphate, acetyldihydrocodeine hydrochloride, codeine, codeine hydrochloride, codeine

[k] Reports contained within Appendices H, I and J may contain duplicates due to overlapping preferred terms within the search strategy that may have been reported within one report.

Table 9. FAERS Search Strategy for Pediatric Reports of Substance Abuse with Codeine-containing Products with a Serious Outcome*	
	phosphate, codeine phosphate anhydrous, codeine polistirex, codeine sulfate, dihydrocodeine, dihydrocodeine bitartrate, dihydrocodeine phosphate
MedDRA search terms (Version 18.0)	SMQ: Drug abuse and dependence††
Age range	18 years of age and below
* See Appendix D for a description of the FAERS database. † Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. Reports may include multiple outcomes. †† See Appendix J, Section 7.10.4 for a description of PTs listed under SMQ: Drug abuse and dependence.	

7.10.3 *Results*

This section summarizes the substance abuse reports in aggregate. These summaries use crude counts of reports and may contain duplicate reports. A full analysis of the potential relationships between codeine-containing products and the adverse events reported in the individual reports was not conducted.

The FAERS search retrieved 212 pediatric reports with codeine-containing products with a serious outcome based on the search strategy described in Table 5. One hundred and twelve (112) reports were domestic reports. Acetaminophen with codeine was the most widely used product and accounted for 138 of the 212 reports.

Among the 212 reports, the reports that were not summarized within the respiratory depression and respiratory distress sections can be categorized as the following:

- Overdose – polysubstance abuse or drug dependence; 63 reports had a death outcome in children ages 11-18
- Suicidality – intentional overdoses, suicide attempts, suicidal ideation and completed suicides; 22 reports had a death outcome in teenagers ages 12-18
- Breastmilk exposure – 4 reports had a death outcome; 3 duplicates; 1 report of ultra-rapid metabolizer mother who received acetaminophen with codeine for episiotomy pain
- Child abuse – 2 reports had a death outcome

Reviewer comment: A majority of the death reports involved children ages 11-18 years and were associated with concurrent use of benzodiazepines, antidepressants or other opioids..

7.10.4 *List of Preferred Terms associated with Standardised MedDRA Query used for Substance Abuse search*

SMQ	PT

SMQ	PT
Drug abuse and dependence	Dependence, Disturbance in social behaviour, Dopamine dysregulation syndrome, Drug abuse, Drug abuser, Drug administered at inappropriate site, Drug dependence, Drug dependence, antepartum, Drug dependence, postpartum, Drug detoxification, Drug diversion, Drug level increased, Drug screen, Drug screen positive, Drug tolerance, Drug tolerance decreased, Drug tolerance increased, Drug level above therapeutic, Intentional overdose, Intentional product misuse, Intentional product use issue, Maternal use of illicit drugs, Medication overuse headache, Narcotic bowel syndrome, Needle track marks, Neonatal complications of substance abuse, Overdose, Polysubstance dependence, Prescribed overdose, Prescription form tampering, Substance abuse, Substance abuser, Substance use, Substance-induced mood disorder, Substance-induced psychotic disorder, Toxicity to various agents

7.11 APPENDIX K. FAERS CASE NUMBERS AND MANUFACTURER CONTROL NUMBERS FOR RESPIRATORY DEPRESSION CASE SERIES

FAERS Case Number	Manufacturer Control Number
10078284	AU-RANBAXY-2014RR-80187
10078285	AU-RANBAXY-2014RR-80192
10078286	AU-RANBAXY-2014RR-80188
10078287	AU-RANBAXY-2014RR-80190
10078288	AU-RANBAXY-2014RR-80191
10078290	AU-RANBAXY-2014RR-80186
10078292	AU-RANBAXY-2014RR-80189
10280898	
10661358	ES-JNJFOC-20141203617
10793463	CHPA2015US002016
3036365	WAES 98050823
3647295	01-016
3956640	2003CG00795
3958092	EMADSS2003004374
3983066	03P-163-0225176-00
4107655	
4293693	
4648993	83258111
4677906	M890139
4746652	890249001B
4840054	891318003J
5148778	
5496408	
5709650	
5788170	2005AL001381
5918504	US-JNJFOC-20051100419
5967315	MK200601-0089-1
5992528	HQWYE623501FEB06

FAERS Case Number	Manufacturer Control Number
6168911	
6365935	US-ROXANE LABORATORIES, INC-2007-DE-04207GD
6454487	2007333186
6479378	FR-BAXTER-2007BH009247
6516302	FR-ABBOTT-07P-056-0431041-00
6876687	CA-JNJFOC-20090100502
6959752	DE-ROXANE LABORATORIES, INC.-2009-RO-00318RO
6959806	DE-ROXANE LABORATORIES, INC.-2009-RO-00317RO
7272513	US-JNJFOC-20100201682
7359164	GB-WATSON-2010-05110
7371901	
7453259	GB-RANBAXY-2010RR-35313
7622403	GXKR2010CA11042
7644955	GB-JNJFOC-20101006345
7935926	US-ENDO PHARMACEUTICALS INC.-PMVC20110001
8430100	US-PFIZER INC-2012049990
8522044	CA-ROXANE LABORATORIES, INC.-2012-RO-01056RO
8676907	CA-RANBAXY-2012US-57989
8749396	2012MA009095
8750518	
8756198	
8760324	
8783255	BR-JNJFOC-20120902272
8916728	US-PFIZER INC-2012287198
8927938	
9004632	
9165725	
9232855	
9341300	
9379348	CHER20130002
9382047	US-ROXANE LABORATORIES, INC.-2013-RO-01076RO
9397006	
9423703	PHHY2013GB079457
9443899	US-JNJFOC-20130800666
9856393	US-ROXANE LABORATORIES, INC.-2014-BI-03600GD
9856399	US-ROXANE LABORATORIES, INC.-2014-BI-03598GD

7.12 Appendix L: Tables for Epidemiological Adverse Drug Events

Table L.1. Detailed Description and Frequency of Adverse Effects for Codeine-containing Pediatric ED Visits

Codeine-containing Cough and Cold ED Visits	
Manifestation	**Number of Events**
Abdominal Pain/Epigastric Discomfort	2
Bronchospasm/Dyspnoea (difficult or labored breathing)	1
Dizziness	1
Dystonia (involuntary muscle contraction)	1
Nausea/Vomiting	1
Somnolence	1
Syncope (fainting)	1
Visual Hallucination*	1
Total	**9**
Codeine-containing Analgesic ED Visits**	
Manifestation	**Number of Events**
Vomiting	29
Nausea	22
Abdominal Pain	13
Dyspnoea	8
Chest Pain	5
Constipation	5
Epigastric Discomfort	5
Dizziness	3
Syncope	3
Dehydration	2
Fall	2
Gastritis	2
Pruritus	2
Somnolence	2
Tachycardia	2
Throat Tightness	2
Abnormal Behavior	1
Anger	1
Anorexia	1
Anxiety	1
Depressed Level of Consciousness	1
Drug Intolerance	1

Dyspepsia	1
Emotional Disorder	1
Faecaloma	1
Feeling Hot	1
Hallucination, Visual	1
Headache	1
Heart Rate Increased	1
Hyperhidrosis	1
Laceration	1
Mood Swings	1
Palpitations	1
Presyncope	1
Reflux Gastritis	1
Respiration Abnormal	1
Respiratory Rate Decreased	1
Sedation	1
Tachypnoea	1
Total	130

8 REFERENCES

[1] Williams DG, Hatch DJ, Howard RF. Codeine phosphate in paediatric medicine. Brit J Anaest, 2001; 86; 413-21.

[2] Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450 2D6 Genotype and Codeine Therapy: 2014 Update. Clinical Pharmacology & Therapeutics, Apr 2014; 95(4): 376-382.

[3] Kirchheiner J, Schmidt H, Tzvetkov M. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. The Pharmacogenomics Journal, Jul 2006; Vol 7: 257-265.

[4] FDA Drug Safety Communication. Codeine use in certain children after tonsillectomy and/or adenoidectomy may lead to rare, but life-threatening adverse events or death. August 15, 2012. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm313631.htm.

[5] FDA Drug Safety Communication. Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy. February 20, 2013. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm339112.htm.

[6] April 22, 2015, EMA Communication [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Codeine_containing_medicinal_products_for_the_treatment_of_cough_and_cold_in_paediatric_patients/human_referral_prac_000039.jsp&mid=WC0b01ac05805c516f]

[7] FDA Public Health Advisory. Use of Codeine By Some Breastfeeding Mothers May Lead To Life-Threatening Side Effects In Nursing Babies. August 17, 2007. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm054717 htm.

[8] FDA Drug Safety Communication. Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy. February 20, 2013. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm339112.htm.

[9] Randall T, Choi L, Brinker A. Pharmacovigilance Review: Codeine deaths and overdoses. August 9, 2012

[10] FDA Drug Safety Communication: Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy, 20 Feb 2013. [http://www.fda.gov/Drugs/DrugSafety/ucm339112.htm]

[11] EMA. Codeine not to be used in children below 12 years for cough and cold, 24Apr2015. [http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2015/04/WC500186162.pdf]

[12] FDA Drug Safety Communication. Codeine Cough-and-Cold Medicines in Children: Drug Safety Communication - FDA Evaluating Potential Risk of Serious Side Effects. July 1, 2015. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm453379.htm.

[13] Source: IMS Health, IMS National Sales Perspectives™. Year 2014. Data extracted August 2015. File: NSP 2015-1124 total codeine channel 8-17-2015.xlsx

[14] Phenergan with Codeine [package insert]. Baltimore, MD: BayPharma, Inc; May 2013.

[15] Randall T, Choi L, Brinker A. Pharmacovigilance Review: Codeine deaths and overdoses. August 9, 2012.

[16] FDA Drug Safety Communication: FDA evaluating the potential risks of using codeine cough-and-cold medicines in children; 1 Jul 2015. http://www.fda.gov/Drugs/DrugSafety/ucm453125.htm

[17] Ferreiros N, Dresen S, Hermanns-Clausen M, et al. Fatal and severe codeine intoxication in 3-year-old twins – interpretation of drug and metabolite concentrations. Int J Legal Med, 2009: 123:387-394.

[18] Friedrichsdorf SJ, Postier Nugent A, Stobl A. Codeine-associated pediatric deaths despite using recommended dosing guidelines: Three case reports. Journal of Opioid Management, Mar-April 2013: 9(2): 151-155.

[19] Kravath R, Pollak C, Borowiecki B, Weitzman E. Obstructive sleep apnea and death associated with surgical correction of velopharyngeal incompetence. Journal of Pediatrics, April 1980: 96(4): 645-648.

[20] Randall T, Choi L, Brinker A. Pharmacovigilance Review: Codeine deaths and overdoses. August 9, 2012.

[21] Friedrichsdorf SJ, Postier Nugent A, Stobl A. Codeine-associated pediatric deaths despite using recommended dosing guidelines: Three case reports. Journal of Opioid Management, Mar-April 2013: 9(2): 151-155.

[22] Winek C, Wahba W, et al. Winek's Drug & Chemical Blood-Level Data 2001. http://fscimage.fishersci.com/webimages_FSC/downloads/winek.pdf (Accessed September 14, 2015)

[23] Meyer D, Tobias J. Adverse effects following the inadvertent administration of opioids to infants and children. Clinical Pediatrics , 2005 Jul-Aug; 44(6): 499-503.

[24] Friedrichsdorf SJ, Postier Nugent A, Stobl A. Codeine-associated pediatric deaths despite using recommended dosing guidelines: Three case reports. Journal of Opioid Management, Mar-April 2013: 9(2): 151-155.

[25] Jhung MA, Budnitz DS, Mendelsohn AB, et al. Evaluation and overview of the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project (NEISS-CADES). Med Care 2007; 45(suppl 2):S96-102

[26] Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. JAMA 2006; 296:1858-66. Available at: http://jama.jamanetwork.com/article.aspx?articleid=203690

[27] Schroeder TJ, Ault K. National Electronic Injury Surveillance System (NEISS) sample design and implementation from 1997 to present. Washington, DC: US Consumer Products Safety Commission; 2001. Available at: http://www.cpsc.gov/neiss/2001d011-6b6.pdf.

[28] Prows CA, et.al. Codeine-Related Adverse Drug Reactions in Children Following Tonsillectomy: A Prospective Study Laryngoscope, 124:1242–1250, 2014

[29] Prows CA, et.al. Codeine-Related Adverse Drug Reactions in Children Following Tonsillectomy: A Prospective Study Laryngoscope, 124:1242–1250, 2014.

[30] 2012-1989: NEISS-CADES Search: identify additional cases of death or overdose among children who had recent treatment with codeine, Epperly H

[31] Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450 2D6 Genotype and Codeine Therapy: 2014 Update. Clinical Pharmacology & Therapeutics, April 2014; 95(4): 376-382.

[32] Jungquist C. Risk Factors for Opioid-Induced Excessive Respiratory Depression. Pain Management Nursing, 2011 Sept; 12(3): 180-187.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 June 2013
EMA/441891/2013

Assessment report for codeine-containing medicinal products indicated in the management of pain in children

Procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure number: EMEA/H/A-31/1342

Assessment Report as adopted by the PRAC with all information of a confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

1. Background information on the procedure

Concerns regarding opioid toxicity and the lack of consistent risk minimisation measures were raised following cases described in the literature of morphine toxicity in children treated with codeine after undergoing tonsillectomy for obstructive sleep apnoea. A number of the children were subsequently found to be ultra-rapid or extensive codeine-to morphine metabolisers.

In light of the above, the United Kingdom initiated a procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data and referred the matter to the Pharmacovigilance Risk Assessment Committee (PRAC), on 03 October 2012. On 22 October 2012, an amended notification was received from the United Kingdom, extending the scope of the referral to all types of pain. The PRAC was requested to give its opinion on whether the marketing authorisations for codeine-containing medicinal products indicated in the management of pain in children, should be maintained, varied, suspended or withdrawn. As the request results from the evaluation of data resulting from pharmacovigilance activities, the PRAC should issue a recommendation to the Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMDh).

After reviewing all the available data to address the concerns discussed, the PRAC adopted its recommendation on 13 June 2013.

2. Scientific discussion

2.1. Introduction

Codeine-containing products are authorised nationally in Europe and are indicated for the management of pain in adults and children. They are commonly used in combination with other analgesics such as non-steroidal anti-inflammatory drugs and non-opioid analgesics with the aim of increasing the analgesic effect due to the different mode of action of the individual drugs. The main pharmaceutical form is tablets (60%) but codeine is also available as capsules, effervescent tablets, syrups, suppositories and solutions.

The Pharmacovigilance Risk Assessment Committee (PRAC) noted that in November 2007, the Medicines and Healthcare products Regulatory Agency (MHRA) issued a Drug Safety Update containing a communication on the “very rare risk of side-effects in breastfed babies” from maternal ingestion of codeine, following a 2006 published case report of respiratory depression resulting in death in a breastfed newborn whose mother was a CYP2D6 ultra-rapid metaboliser. The PRAC also noted that in August 2012 the United States (US) Food and Drug Administration (FDA) issued a communication concerning codeine use in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, following reports of rare but life-threatening adverse events, including death. The FDA identified three paediatric deaths and one non-fatal but life-threatening case of respiratory depression, documented in the medical literature (*Ciszkowski C. et al* N Engl J Med 2009 and *Kelly LE et al* Pediatrics 2012). The children ranged in age from two to five years old. The three deaths occurred in children who had evidence of being UMs and the life-threatening case occurred in a child who was an extensive metaboliser. All children received doses of codeine that were within the recommended posology; however the post-mortem morphine concentrations in the three children who died were substantially higher than the recommended therapeutic range. Following its review, the FDA concluded that there was a need to add a boxed warning and a contraindication to the product information of US products against the use of codeine for the post-operative pain management in children after tonsillectomy or adenoidectomy, regardless of the metabolic status.

The PRAC discussed this issue during its September 2012 meeting and concluded that since 2007, there were five cases of opioid toxicity in children treated with codeine after undergoing tonsillectomy for obstructive sleep apnoea, with a sixth, non-fatal case reported in 1997 (*Talbott et al*, 1997). Three of the children were subsequently found to be CYP2D6 extensive or ultra-rapid metabolisers. The PRAC therefore concluded that the issue of serious opioid toxicity and the lack of consistent risk minimisation measures should be evaluated fully in order to determine whether further risk minimisation measures should be introduced in order to ensure the safe use of codeine. In October 2012, a referral under Article 31 of Directive 2001/83/EC was therefore initiated. The PRAC was therefore specifically

requested to assess all available evidence of the efficacy and safety of codeine and thus review the benefit-risk balance of codeine-containing medicinal products (including combination products) indicated in the management of pain, including post-operative analgesia, in children.

The PRAC adopted a list of questions to be addressed by all marketing authorisation holders (MAHs) of codeine-containing medicinal products indicated in the treatment of pain in children. The MAH responses included searches of Medline (via Ovid or PubMed), Embase, Google Scholar and Cochrane reviews, summaries of relevant studies and data from pharmacovigilance databases. Following the review of the MAH responses, the PRAC noted differences across the member states with regard to the wording of the indication (details of the type and intensity of the pain), posology, contraindications and warnings and the mention of CYP2D6 genetic polymorphisms.

2.2. PRAC review of clinical efficacy

2.2.1. Pharmacogenetics, pharmacokinetics and pharmacodynamics of codeine metabolism

The analgesic properties of codeine stem from its conversion in the liver to its active metabolite morphine by the hepatic microsomal enzyme system cytochrome P450 enzyme CYP2D6. The toxicity of codeine is mainly due to its opioid effects and the most common adverse reactions to codeine include drowsiness, light-headedness, dizziness, sedation, shortness of breath, nausea, vomiting, and sweating, while serious adverse reactions include respiratory depression and, to a lesser degree, circulatory depression, respiratory arrest, shock, and cardiac arrest.

It has been established that CYP2D6 is subject to extensive polymorphism resulting from more than 100 different known allelic variants. This phenotypic variability is translated into a wide spectrum of metabolic capacity in terms of the capacity to metabolise codeine. Broadly speaking, CYP2D6 alleles are characterised as wild-type (normal function), reduced-function, or non-functional based on the expected activity level of the enzyme for which they encode. Two non-functional alleles result in poor metaboliser (PM) phenotype; at least one reduced functional allele in intermediate metaboliser (IM); at least one functional allele in extensive metaboliser (EM) and multiple copies of a functional allele, due to duplication or multi-duplications of the CYP2D6 gene, in ultra-rapid metaboliser (UM) phenotype (*Somogyi et al.*, 2007, *Madadi P et al*, 2008; *Ingelman-Sundberg M et al*, 2007). The clinical implications of this genetic polymorphism are not fully understood but have been reported in the literature to be linked to potentially serious events of opioid toxicity, as described in this report. Ultra-rapid codeine metabolism in UM patients may result in increased conversion of codeine to morphine resulting in toxic systemic concentrations of morphine even at low codeine doses. On the other hand, a lack of analgesic efficacy can occur in PM patients, even at high doses, making it impossible to predict treatment response and the risk of opioid intoxication, even if the patient's CYP2D6 status is known.

The PRAC noted that prevalence of the various phenotypes varies across individuals, based on ethnicity and has been determined for a number of ethnicities and nationalities. 7–10% of Caucasians are PMs, while the prevalence is 2% of Asians and 1% of Arabs. Regarding UMs, the overall prevalence in Caucasians is up to 10% but ranges from low in northern Europe (1-2% in Finland, Denmark, Norway and Sweden), Central Europe, North America (4-5%) and Asia (0.5-2.5%), to significantly higher in the Mediterranean countries (7-12% in Portugal, Spain, Greece and Italy), Saudi Arabia (21%) and Ethiopia (29%). Overall, it is estimated that the distribution of CYP2D6 phenotypes is the following: 1.9% UM, 6.5% IM, 8.3% PM, and 83.3% EM (*Rideg et al*, 2011).

The PRAC noted the literature reviews carried out by the MAHs of studies which investigate the use of codeine as an analgesic, both in adults and in children, including studies investigating the route of administration. The vast majority of pharmacokinetic (PK) and pharmacodynamic (PD) data for codeine has been obtained from investigations in adults, very little information is available from studies in children or infants and no published work in neonates was identified. Overall PK and PD studies in children are lacking, particularly regarding the impact of the CYP2D6 genetic polymorphism on the efficacy of codeine in analgesia.

When considering the studies conducted in adults, the PRAC noted in particular the Clinical Pharmacogenetics Implementation Consortium (CPIC) systematic review relating to the interpretation

of CYP2D6 genotype test results to guide the dosing of codeine (*Crews KR et al* 2012). The resulting guidelines give a strong recommendation to avoid codeine use in patients with known CYP2D6 UM and PM phenotypes and to consider alternative analgesics such as morphine or non-opioids. CYP2D6 phenotypes can be predicted, although not fully, from CYP2D6 genotypes. In addition, the study by *Kirchheiner et al* (2007) investigated the PK differences of codeine between a group of UMs and EMs. A small group of PMs served as an additional reference group. A single dose of 30mg codeine was administered. Significant differences between the EM and UM groups were detected in areas under the plasma concentration versus time curves (AUCs) of morphine. The authors observed a strong correlation between the number of active CYP2D6 genes and plasma concentrations as well as urinary recovery ratios of codeine metabolites. The plasma concentrations and AUCs of morphine between UMs and EMs differed about 1.5-fold with a nearly exact linear gene-dose effect. CYP2D6 genotypes predicting UMs resulted in about 50% higher plasma concentrations of morphine and its glucuronides compared with the EMs. No severe adverse effects were seen in the UMs in the study, most likely because a low dose of only 30 mg was used for safety reasons.

The studies conducted in children were also reviewed. The PK/PD study conducted by *Williams DG et al* (2002) was considered to be of high relevance. It investigated genotype, phenotype and morphine production from codeine in 96 children aged from three to 12 years undergoing adenotonsillectomy, and compared analgesia from codeine or morphine combined with diclofenac. The study concluded that a reduced ability to metabolise codeine may be more common than previously reported and considerably higher than the prevalence described for the general population.

The PRAC concluded that as the inter-individual variability of response to codeine analgesia is related to functional polymorphisms in CYP2D6, PMs may suffer from poor analgesia with codeine but still experience some adverse effects, while UMs may experience exaggerated and even potentially dangerous opioid effects, although the variability of the analgesic effect which can be attributed to CYP2D6 genotypes has not been completely defined in the paediatric clinical settings. Assays are available to determine the genotype of the key pathways involved in codeine bioactivation but while it acknowledged that CYP2D6 genotyping prior to analgesic therapy is desirable where accurate testing is available, the PRAC considered that this is unlikely to happen in most clinical practice, particularly as the response to codeine is not directly correlated with phenotype. Close monitoring for signs of opioid toxicity is therefore of critical importance. The study by *Williams et al* on the implications of CYP2D6 polymorphisms on the analgesic effect of codeine found similar associations between serum metabolite concentrations and phenotypes, however no differences in pain scores or need for a rescue medication after codeine administration were identified for the different phenotypes in children.

2.2.2. Effect of age on the efficacy of codeine

It has been suggested that infants and neonates have a reduced metabolic capacity for codeine as CYP2D6 activity is absent or less than one per cent of adult values in foetal liver microsomes. Some authors consider that CYP2D6 expression rapidly reaches adult levels within the first 6 months after birth (*Stevens JC et al* 2008), while others suggest that enzyme activity may still be less than 25% of the adult values up to 5-years of age (*Tateishi T et al* 1997). The effect of age was examined in a study by *Quiding et al* (1992). The study investigated whether infants and young children are capable of demethylating codeine to morphine. Thirteen infants and young children participated in the study. Nine were between six and ten months old and four were between three and four years old. The study concluded that at the age of six months, infants are capable of demethylation of codeine to morphine. Codeine administered rectally in infants at 0.5 mg/kg and in older children at 8 mg resulted in similar plasma concentrations of codeine and morphine as 60 mg codeine administered orally to adults. The mean half-life was found to be 2.6 hours, but in infants with the lowest weight, the half-life was over two hours longer than this value.

The PRAC concluded that the influence of childhood development on the efficacy and side-effects of codeine has not been well-investigated. In summary, the limited data available appear to suggest that the PK of codeine and its active metabolite morphine may be similar in older children and adults; however the data is largely inconclusive. The evidence suggests that children are capable of demethylating codeine to morphine at the age of six months. However, glucuronidation in younger children may be impaired, resulting in an additional influence on the unpredictable metabolism of

codeine. As a result, caution should be applied when interpreting the effect of age and consideration should be given not only to genetic polymorphism but also the increasing enzymatic activity with age. Moreover, the rate at which most drugs are absorbed is generally slower in younger children, particularly if unwell or under sedation so the time to achieve maximum plasma concentrations may be prolonged. *Bhat R et al* (1996) studied morphine metabolism in acutely ill preterm newborn infants and concluded that nearly two thirds of acutely ill preterm infants born at less than 32 weeks of gestational age conjugate morphine. However, irrespective of their ability to produce morphine conjugates, preterm infants excrete large amounts of morphine unmetabolised, as late as 24 hours after a single dose and morphine handling patterns are highly variable among premature infants. The authors proposed that variability in morphine handling in general and the production of the highly potent morphine-6-glucuronide in particular could explain the variance in morphine pharmacokinetic measures and in the clinical responses to morphine during the newborn period. Therefore, the PRAC raised concerns that when codeine is used in very young children, the lack of a clinical response to the medication as a result of slower absorption could lead to unnecessary and potentially harmful dosing adjustments. For products with age restrictions, it was noted that a cut-off age of 12 years was stated in the majority of the SmPCs, based on a lack of established safety and efficacy of codeine. The PRAC regarded this age restriction as adequate, taking into account the reviewed data suggesting that the enzymatic system responsible for the metabolism of codeine can be considered fully matured by the age of 12.

2.2.3. Efficacy data

The PRAC reviewed the available data on the efficacy of codeine, including in combination products. Studies conducted in children compared codeine alone or in combination with ibuprofen, paracetamol and morphine for indications such as musculoskeletal injuries, fracture, neurosurgery, and post-operative pain-relief. Most of these trials suggested comparable efficacy of codeine with other active treatments, although for musculoskeletal pain/extremity injuries, NSAIDs were shown to have equal or better efficacy compared to codeine/paracetamol (*Drendel AL et al*, 2006; *Friday JH et al* 2009; *Drendel AL et al* 2009; *Clark E et al* 2007, *Charney RL et al* 2008, *Swanson CE et al* 2012).

The PRAC also reviewed studies on the use of codeine for post-surgical pain relief in children, mostly after tonsillectomy or other ear, nose and throat (ENT) operations, after neurosurgery and also for dental extraction. Overall, these studies showed that paracetamol with codeine provides effective analgesia in children. Studies in neurosurgery by *Ou et al* (2008), *McEwan et al* (2000), (*Warren et al*, 2010) and *Teo JH et al* (2001) and concluded that there is no strong evidence suggesting that the use of codeine plus paracetamol is a safer or more efficacious choice compared to morphine in paediatric patients undergoing neurosurgical procedures. Studies in ENT by *Tremlett et al* (2010), *Khetani JD et al* (2012), *Subraamanyam R et al* (2012), *Rawlinson E et al* 2011 and *Harley et al* (1998) showed a reluctance of clinicians to prescribe NSAIDs following tonsillectomy due to the risk of bleeding, although this risk was inconsistent with other similar paediatric studies by *Charles et al* (1997), *Shaikh et al* (2011), *Tobias J et al* (1995), *St Charles CS et al* 1997), *Semple D et al* (1999), *Moir MS et al* (2000), *Ewah BN et al* (2006) and *Pappas AL et al* (2003).

The PRAC considered that the available studies are small and offer limited information regarding the efficacy of codeine in post-operative analgesia as there are no studies identified using codeine as a single analgesic compared against placebo. In the presented studies, the clinical efficacy of codeine was mostly assessed in combination with paracetamol and compared to other medications (ibuprofen, paracetamol alone, morphine etc.) in various clinical settings. In the studies in children with skeletal trauma, it was concluded that ibuprofen has efficacy comparable to codeine in combination with paracetamol when used for acute paediatric arm fracture pain, acute traumatic extremity pain and outpatient fracture pain. However, for acute paediatric arm fracture pain, the side effects were fewer with ibuprofen use compared to the use of codeine with paracetamol. In paediatric tonsillectomies and/or adenoidectomy, no significant differences between treatments were demonstrated. Pain appeared to worsen after operation within the first five days post operatively. However one study showed that codeine plus paracetamol had a better analgesic effect compared to ibuprofen in the first two to three post-operative days but that there was no difference between treatments at day five (*Harley et al* 1998). The type of operation (coblation or electrocautery tonsillectomy) has to be taken

into consideration both in term of analgesia required and the risk of post-operatively bleeding. *Parker and Walner* (2011) found that the average number of post-operative days with severe pain was 4.2 for coblation and 5.9 for electrocautery (P = 0.006), days rating pain ≥ 5 were 3.6 for coblation and 4.8 for electrocautery (P = 0.037), days of codeine use were 2.5 for coblation and 2.9 for electrocautery (P = 0.324), and days until resumption of a regular diet were 5.2 for coblation and 6.2 for electrocautery (0.329). The use of ibuprofen is associated with good pain control after tonsillectomies, however it has been linked to an increased risk of bleeding, albeit not clearly established. Interestingly, a study found that parents indicated that they would accept a higher bleeding risk (3%) for their children in exchange for better pain control (*Low TH et al* 2009). Furthermore, a study by *Khetani et al* (2012) explored the respiratory risks for patients undergoing adenotonsillectomies for obstructive sleep apnoea (OSAS). The authors stated that the lack of improvements in rates of saturation observed the day after surgery may be due to residual effect of the anaesthetics, presence of blood or oedema in the area of surgery as well as increased airway compliance and decreased airway neuromuscular function in children with OSAS. However the fact that in certain cases the rates of apnoea rose dramatically during the night following surgery suggest that the prescribed opioids may have exerted respiratory depression in some children. The PRAC was concerned by these findings in paediatric patients undergoing tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome.

With regards to dose, limited data is available from studies in children, and the posology is mostly extrapolated from results observed in adults. Doses such as 30 to 60 mg every six hours, with a maximum daily dose of codeine of 240 mg are usually recommended while higher doses cannot be routinely recommended in the absence of additional efficacy and safety data. A British guideline stated that the recommended use of codeine for short-term treatment of moderate pain involves a dosing schedule based on body weight of 0.5-1 mg/kg 4-6 hourly in neonates and paediatric patients. The PRAC noted that in children, this represents doses of 30 to 60 mg every six hours. The duration of use should be limited to three days, after which the need for alternative treatment should be considered.

2.2.4. PRAC conclusions on clinical efficacy

Based on the available efficacy data the PRAC therefore concluded that there is no strong evidence of a superior analgesic profile of codeine compared to other analgesics such as non-steroidal anti-inflammatory drugs and non-opioid analgesics in the management of post-operative pain in children, although it is recognised that codeine containing medicinal products have demonstrated efficacy in the treatment of acute moderate pain that is not solely relieved by other analgesics such as paracetamol and ibuprofen. The PRAC noted that the analgesic effect of codeine equals approximately 1/10th that of morphine, making it suitable for mild to moderate pain but unsuitable for severe or chronic pain, even in larger doses.

The genetic polymorphism of CYP2D6 was considered to be clinically relevant to the efficacy and safety profile of codeine in the paediatric population, as the prevalence of a reduced ability to metabolise codeine may be more common in children than in the general population. The limited data available also suggests that the activity of CYP2D6 increases markedly after birth but remains inferior to the activity of adults, which may result in lower analgesic effect. Clinicians prescribing codeine should consider the potential for a reduced response leading to an inadequate analgesic effect in some children. The enzymatic system responsible for the metabolism of codeine can be considered to be fully matured by the age of 12, with comparable metabolic behaviour to that of adults, in terms of drug absorption, distribution and renal clearance. In addition, enhanced adverse effects may be observed in patients which are ultra-rapid metabolisers (resulting in higher than expected serum morphine levels) and therefore clinicians should be highly alert to the signs and symptoms of opioid toxicity.

Doses are typically extrapolated from adult data and doses such as 30 to 60 mg every six hours, with a maximum daily dose of codeine of 240 mg are usually recommended. Higher doses, however, cannot be routinely recommended in the absence of additional efficacy and safety data. This is particularly important due to the confirmed risk associated with administration of codeine in UMs. The PRAC considered that if no effective pain relief is observed after a period of three days, a revision of the treatment needs to be considered.

2.3. PRAC review of clinical safety

The PRAC noted that the MAHs did not conduct any preclinical, clinical or pharmacoepidemiological studies in the context of this review and all the evidence provided was collected from post-marketing spontaneous reports, including reports published in the literature. No preclinical data to support the use of codeine in the paediatric population was submitted.

2.3.1. Summary of serious and fatal paediatrics reports

The PRAC reviewed the 6 cases (including three with a fatal outcome) of opioid toxicity in children aged two to five years who were treated with codeine after undergoing tonsillectomy for obstructive sleep apnoea, as identified by *Talbott et al* (1197), *Voronov et al* (2007), *Ciszkowski et al* (2009) and *Kelly et al* (2012). All children received codeine at recommended dose and where known, the children were subsequently found to be either ultra-rapid or extensive metabolisers. Since these children had underlying breathing problems, it has been suggested that they may more sensitive to developed respiratory depression when codeine converts to high levels of morphine.

In addition, 14 fatal cases were identified in EudraVigilance where codeine was used for analgesia in paediatric patients. Most of the cases are scarcely documented. In 3 cases, the cause of death was an underlying disease, in one case an accidental overdose and in another one death was related to paracetamol (hepatic failure).The remaining cases involved patients from 2 to 17 years of age. Half of the cases occurred in children between 2 and 6 years of age. Toxic morphine levels were reported in 4 cases, and in 2 cases children appeared to receive codeine in the range of the recommended dose. Genotype/phenotype was not available. Indications were AT (2 cases), headache (1 case) sporting injury (1 case), aphthous stomatitis (1 case) and unknown in the remaining cases.

Cases associated with codeine exposure through breastfeeding were reviewed to investigate whether breast-fed infants of mothers taking codeine could be at an increased risk of opioid toxicity if the mother was an ultra-rapid metaboliser. In a report by *Koren G et al* (2006), a 13-day-old infant experienced respiratory depression resulting in death after being exposed to morphine in his mother's breast milk; the mother had been taking oral codeine 30mg and paracetamol 500mg twice daily for episiotomy pain for about two weeks. The clinical and laboratory picture was consistent with opioid toxicity leading to neonatal death. Assayed morphine concentrations in the breast milk were found to be 87 ng/mL, compared to the usual range of 1.9 to 20.5 ng/mL after repeated doses of codeine 60mg four times daily. Subsequent investigations found that the mother's genotype for the cytochrome P450 isoenzyme CYP2D6 classified her as an ultra-rapid metaboliser.

A review of 72 mother–child pairs showed that 17 (24%) breastfed infants exhibited central nervous system depression while their mothers used codeine (*Madadi P et al*. 2009). Ultra-rapid metabolisers were identified in 3 (11.8%) cases. One case was asymptomatic, of the other two, one was described previously (*Koren G et al* 2006) and the second was a mother who used 120 mg/day codeine for severe muscle pain after childbirth. Her breastfed infant was described as extremely drowsy and feeding poorly. She began supplementing breast milk with formula after delivery because of personal exhaustion and due to her infant’s feeding difficulties. On the seventh day after delivery, the mother had switched completely to formula feeding and a complete reversal of the infant’s symptoms was noted in the following days.

A further review by *Madadi et al* (2012) identified 44 cases of neonatal respiratory depression in breastfeed infants of mothers who were using codeine.

Although it was acknowledged that opioid toxicity may occur at all ages, the PRAC concluded that the current evidence suggests that children are at special risk of life-threatening or fatal respiratory depression in association with the treatment of pain with codeine, particularly the specific subpopulation of patients who might already have a compromised airway and require post-operative pain relief.

In addition, the PRAC noted an abstract citing four near-term breastfed infants who exhibited neonatal apnoea attacks which started 4–6 days following administration of 60 mg codeine (q 4–6 h) to breastfeeding mothers (Davis JM et al, 1985) and an abstract reporting that 10 of 12 full-term infants who had unexplained episodes of apnoea, bradycardia, and/or cyanosis occurring in the hospital

between 0.5 and 7 days of age were exposed to opioids through breast milk, with six of the infants specifically exposed to codeine in breast milk (Naumburg EG, 1987).

A study by *Willmann S et al* (2009) which investigated the risk of opioid poisoning to breast-fed neonates using coupled physiologically-based pharmacokinetic models for the mother and child was also considered in the review. The simulations demonstrated that the mother's codeine and morphine clearances and the neonate's morphine clearance are the most critical determinants of morphine accumulation in the neonate and that given the added effect of low neonatal elimination capacity for morphine, potentially toxic morphine plasma concentrations can be reached within four days in the neonate after repeated codeine dosing to the mother. Neonates of mothers with the UM CYP2D6 genotype and neonates of mothers who are EMs had comparable risks of opioid poisoning.

Regarding the risk of trans-placental exposure to codeine, the PRAC noted a study by *Nezvalová-Henriksen K et al* (2011) which analysed the effect of codeine on pregnancy outcome in a large population-based cohort study (2,666 women who used codeine during pregnancy were compared with 65,316 women who used no opioids during pregnancy). It was concluded that no effects of maternal codeine intake during pregnancy were observed on infant survival or congenital malformation rate.

Finally, the PRAC noted a review by *Neisters et al* (2012) of case reports of opioid-induced respiratory depression (OIRD) in children. Opioid treatment is potentially life-threatening, although there are no numbers available on the incidence of OIRD in paediatrics. To get an indication of specific patterns in the development/causes of OIRD, the authors searched PubMed (May 2012) for all available case reports on OIRD in paediatrics, including patients 12 years of age or younger who developed OIRD from an opioid given to them for a medical indication or due to transfer of an opioid from their mother in the perinatal setting, requiring naloxone, tracheal intubation, and/or resuscitation. Twenty seven (27) cases are described in 24 reports, of which seven cases were fatal. In eight cases, OIRD was due to an iatrogenic overdose. Three distinct patterns in the remaining data set specifically related to OIRD include: (i) morphine administration in patients with renal impairment, causing accumulation of the active metabolite of morphine; (ii) codeine use in patients with CYP2D6 gene polymorphism associated with the ultra-rapid metaboliser phenotype, causing enhanced production of morphine; and (iii) opioid use in patients after adenotonsillectomy for recurrent tonsillitis and/or obstructive sleep apnoea, where OIRD may be related to hypoxia-induced enhancement of OIRD.

2.3.2. PRAC conclusions on clinical safety

Having reviewed the available data on the safety of codeine in paediatric patients, including serious and fatal cases, the PRAC considered that the respiratory depressant effects of opioids may influence the occurrence of respiratory complications and that high levels of morphine as a result of codeine-treatment can result in severe respiratory depression, which can be fatal in some cases. Taking codeine after tonsillectomy and/or adenoidectomy may increase the risk of respiratory depression and subsequently death. This appeared to be of particular concern in children who are ultra-rapid metabolisers although it was acknowledged that the CYP2D6 status was not known in the majority of the serious and fatal cases. In conclusion, the PRAC considered that the review of the cases involving codeine alone or in combinations recorded in post marketing pharmacovigilance databases suggests that codeine may be responsible for opioid toxicity with a possible fatal outcome. The ultra-rapid metaboliser phenotype and young age appear to be risk factors as the majority of all the reported events reviewed occurred in children 0 to 12 years of age and the PRAC therefore concluded that this age group is especially susceptible to the toxic effects of codeine. In addition, the PRAC considered that all paediatric patients who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea or are treated for post-operative pain after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea are at particular risk, given the possibility of respiratory depression.

In order to adequately minimise the risk, the PRAC therefore considered that codeine-containing medicinal products indicated in the management of pain in children should only be administered to children above the age of 12 years of age and contraindicated in all paediatric patients below 18 years of age undergoing tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome, regardless of CYP2D6 status. Warnings on the signs and symptoms of opioid toxicity should be reflected in the product information. In addition, restrictions should be placed on the maximum daily dose and the duration of use.

2.4. Other information relevant to the assessment

2.4.1. Consultation of the Paediatric Committee

The Paediatric Committee (PDCO) was consulted regarding the use of codeine as an analgesic in the paediatric population. It was recognised that the use of codeine varies significantly in paediatric clinical practice across the EU. The risk of morphine intoxication due to genetic polymorphism of its metabolic pathway was discussed and it was noted that the reported cases of severe or fatal adverse drug reactions were limited and mainly identified in young children. The PDCO also discussed the lack of robust evidence of a superior therapeutic effect for codeine when compared to other simple analgesics (i.e. paracetamol and ibuprofen) although it was acknowledged that there is a lack of robust studies investigating the use of codeine in the paediatric population. Concerns were expressed regarding the lack of alternative safe and effective analgesics particularly for younger age groups. The PDCO also supported a contraindication of the use of codeine in all paediatric patients (0 to 18 years of age) that undergo tonsillectomy and/or adenoidectomy for Obstructive Sleep Apnoea Syndrome due to an increased risk of respiratory depression. The PDCO recommended that the risk of codeine's genetic polymorphism should be communicated to healthcare professionals across the EU.

2.4.2. Clinical Practice Research Datalink (CPRD) review of the use of codeine in tonsillectomies and adenoidectomies

As the majority of the adverse events and cases with fatal outcomes following the use of codeine as an analgesic were identified in children undergoing tonsillectomies and adenoidectomies particularly associated with sleep apnoea, the PRAC reviewed specific data extracted from the from the Clinical Practice Research Datalink (CPRD) to estimate how many of these procedures occurred in children in England between 1st January 2009 and 31st December 2011. Data from children aged 18 years or under who had a record of a tonsillectomy, adenoidectomy or dual procedure in the 3-year period were reviewed. The PRAC noted that 5,942 children with a record of a tonsillectomy and/or adenoidectomy were identified during the study period, although the proportion of children with a diagnosis of apnoea was very low. Out of these children, only 77 were prescribed a codeine-containing product in the one month period following the procedure. There were no records of children with a diagnosis of sleep apnoea and who were also prescribed codeine-containing products following their procedure. The PRAC noted that tonsillectomies and/or adenoidectomies occur more commonly in children below the age of 12 years. These patients appeared to be diagnosed with sleep apnoea more frequently than older children but the numbers are overall very low. A survey of paediatric anaesthesiologists in the UK in 1996 (*de Lima J et al*) showed that alongside morphine and fentanyl, codeine is the most widely prescribed opioid analgesic in paediatric anaesthetic practice. However in recent years in the UK, the use of codeine postoperatively has become less common, as indicated by this CPRD review. The PRAC considered that the reason for this decline in use is unclear and commented that one explanation may be that the published reports of fatal cases in these patients have deterred prescribers.

2.4.3. Consultation of the Pharmacogenomics Working Party

The PRAC also consulted the Pharmacogenomics Working Party (PGWP) to obtain input on CYP2D6 phenotype assays and the capacity to predict ultra-rapid metabolisers.

The PGWP noted that besides the therapeutic drug monitoring, CYP2D6 phenotyping allows determination of the actual enzymatic activity by administering a specific probe drug and measuring the concentration of the drug and its metabolite in the urine. This allows the identification of the four previously defined metaboliser groups (UMs, EMs, IMs and PMs). However, it was noted that phenotype prediction according to allele combination is more complex and very different predictive powers are observed depending on the group of metabolisers considered. On the other hand, genotyping allows precise determination of the individual's CYP2D6 DNA sequence and the possibility to predict a phenotype based on the alleles identified. Of note, almost 100% of PMs are identified by genotyping, whereas only 20% of UMs are correlated to an increased number of CYP2D6 gene copies. Reviewing the Rebsamen et al. (2009) publication, the PGWP noted that the AmpliChip CYP450 test is the first genotyping array allowing simultaneous analysis of 33 CYP2D6 alleles, including CYP2D6. The AmpliChip CYP450 test genotyping accuracy for five CYP2D6 alleles was verified (alleles 3,4,5,6, xN;

n=100) and the results confirmed those obtained by real-time PCR. Major improvements using the array are the detection of CYP2D6 intermediate alleles and identification of the duplicated alleles. The CYP2D6 phenotype was determined by assessing urinary elimination of dextromethorphan and its metabolite dextrorphan and compared to the array prediction (n=165). The sensitivity for detecting UM was very low (only 6 %). Therefore, although the genotyping method may predict PM phenotype, the PGWP considered that the method cannot be recommended for UM phenotype prediction. The PGWP considered the publication by *Crews et al* (2012) which recommends using alternative analgesics in patients who are CYP2D6 poor metabolizers or ultra-rapid metabolizers but was of the view that currently, considering the risks of opioid toxicity following the use of codeine in UMs and the lack of practical accurate testing method for the UM status, the risk minimisation measures should include close monitoring of the symptoms and signs of opioid intoxication. The PGWP agreed that the use of codeine in children should be carefully evaluated considering the serious consequences in the reported cases in UMs and that the risk minimization for codeine use should be harmonized in the EU.

2.4.4. EMA analysis of fatal reports in EudraVigilance and case reports in the scientific literature

The PRAC also considered an analysis of fatal cases included in EudraVigilance carried out by the EMA. This EudraVigilance analysis describes the paediatric adverse drug reaction reports where codeine was a suspect or interacting substance. The analysis was based on fatal and non-fatal case reports in the scientific literature and individual case safety reports (ICSR) in EudraVigilance.

A total of fifteen ICSRs reporting fatal cases where codeine was used for analgesia in paediatric patients were identified and reviewed individually. In three cases, codeine did not seem to be a part of the causal mechanism while in the remaining twelve case reports, codeine was considered at least as a contributory cause. Of note, in three of these cases, codeine was considered the cause either due to an accidental overdose, due to the presence of significant baseline risks, such as renal failure, or as a triggering factor for citrullinaemia. In five of the fifteen case reports, codeine was used to manage pain following a surgical procedure, three of which were adenotonsillectomy. In the remaining ten cases, codeine was used either for managing general pain or for an unknown indication. The blood level of codeine was reported in five case reports, of these four were above the toxic threshold whereas one was within normal therapeutic values. Regarding concomitant medications it was noted that in two case reports, fentanyl and in three case reports valproic acid were co-administered.

In addition, eight full text articles (by *Voronov et al* 2007, *Hermanns-Claussen et al* 2008, *Ciszkowski and Madadi*, 2009, *Kelly et al* 2012, *Meyer and Tobias*, 2005, *Magnani and Evans*, 1999, *Talbott et al* 1997 and *Tong and Ng*, 2001) were reviewed, corresponding to 11 individual cases, 6 of which in the indication for analgesia. In the analgesia indication, the age range for the 6 cases of opioid toxicity was from 2 to 5 years-old. The time-to-onset described was under 2 days for all these cases. Most papers provided morphine blood levels and the lowest morphine level in the fatal cases was 17 ng/ml in a 4 year-old which was subsequent to having taken 4 doses of 8 mg. The phenotype was known in all but one case report in the literature, and in all of those the child was a CYP2D6 UM. Additional cases were retrieved from two scientific papers but the full text articles were not available.

In conclusion, opioid toxicity in codeine exposed patients was found to occur either due to toxic levels of morphine in the blood or due to exposure to multiple narcotic analgesics or other drugs that share the same respiratory depression effect. In CYP2D6 UM patients for whom a normal dose of codeine was administered, opioid toxicity may stem uniquely and directly from the fact that these patients metabolise higher proportions of codeine into morphine. Noticeably, in all but one literature papers where the indication was pain management following adenotonsilectomy, the children were found to be CYP2D6 UMs. While this pathological mechanism is well recognised, it even seems unclear whether the kinetics can be predictable, considering the multiple polymorphisms and the influence of ontogeny in these patients. Additionally, other causes for higher blood levels of morphine may be considered, such as the total dose administered, the blocking of other metabolic pathways or the accumulation due to impaired drug elimination routes.

2.4.5. EMA Drug utilisation of codeine in children: analyses of The Health Improvement Network and of the IMS Health German databases

The PRAC also reviewed a drug utilisation analysis investigating the use of codeine in children and the incidence of death occurring within this population, focusing on the tonsillectomy/adenoidectomy indication. The analyses were performed using The Health Improvement Network (THIN) database (UK general practice) and the IMS database (German general and specialists practice). Prevalence data from these sources were also compared with data from Sweden and Denmark. The objectives of the analyses were to estimate prevalence of codeine exposure in children in the UK, DE, SE and DK, the incidence of death in UK children prescribed codeine by different time windows, the cause of death analysis in UK children prescribed codeine and dying within a short time frame and the UK prevalence of prescription of codeine in tonsillectomy and/or adenoidectomy procedures. For both analyses, the study population was defined as less than 20 years old with a prescription of codeine during the study period, to allow comparing the results with Danish and Swedish national data. The study period was defined as 1st January 2001 to 31st December 2011.

The THIN database analysis showed that 91,112 children out of 2,515,938 in THIN were prescribed codeine during the study period. A total of 289 deaths were reported in these children, with 10 deaths occurring within 14 days of codeine prescription but none of these had a reported cause of death related to codeine toxicity. More than 80% of children prescribed codeine received only one codeine prescription during a calendar year and more than 70% received only one codeine prescription during the whole study period. 21,171 tonsillectomy procedures, 7,317 adenoidectomy procedures and 8,254 combined tonsillectomy and adenoidectomy procedures were recorded in the database. Codeine was prescribed in 9% of tonsillectomy procedures and 0.5% of adenoidectomies (within +/- 7 days), with a prescription peak in the period 4 to 7 days post-operatively, which was considered relatively low, although it was noted that codeine prescribed at the hospital during the procedure or codeine given at the hospital is not captured by THIN. In addition, no tonsillectomies and/or adenoidectomies were conducted in these patients within plus/minus 365 days of the final prescription before death, although it was noted that the cause of death is often not recorded in the database. While the date of death is considered reliable, the cause of death had to be found indirectly for a majority of the 10 patients dead within 14 days after a codeine prescription.

The IMS database analysis showed that 59,625 children received at least one prescription of codeine during the study period. In 2011, there were 12,259 codeine-prescribed children, this was 0.34% of the total population of children in 2011 (3,547,640). The total of 99,529 codeine prescriptions to 59,625 children gives an average number of prescriptions per children of 1.67, which indicates that use is predominately acute.

The PRAC noted that the populations analysed were mainly from Northern Europe, were the prevalence of CYP2D6 ultra-rapid metabolisers is the lowest, around 1-4% (Ingelman-Sundberg, 2005). It was also noted that prevalence in THIN is higher for females compared to males (double in 2011), while in IMS prevalence was similar between genders. Both in THIN and IMS, prescription seems predominantly for acute use. The PRAC also noted an analysis conducted using BIFAP (Spanish General Practitioners database), which showed that the overall prevalence of use in children is higher in Spain than in northern countries, with 3.7 users per 100 persons, as per 2011.

2.5. Risk management plan

The PRAC, having considered the data submitted in the application, is of the opinion that the proposed restrictions of use, together with the other changes to be introduced to the product information (PI), will be adequate to address the concerns assessed in this procedure and that no additional risk minimisation activities are required beyond those included in the product information.

2.6. Overall discussion and benefit-risk assessment

Having reviewed the totality of the available data on the efficacy and safety of codeine-containing medicinal products indicated in the management of pain in children, including responses submitted by the marketing authorisation holders (MAHs), the PRAC noted that there is more limited information on

the pharmacokinetics of codeine metabolism in children than is available for adults. The available data suggests that the maturity of the renal system and the drug metabolising enzymes, body weight or composition and the ontogeny of enzymes involved in the metabolism and pharmacology of codeine may be determinant for its analgesic or toxic effect and therefore result in pharmacokinetic differences in children compared to adults and between different age groups of children (neonates, infants).

Regarding efficacy, having reviewed the available efficacy data, the PRAC was of the opinion that the analgesic profile of codeine is not superior to that of other analgesics, such as non-steroidal anti-inflammatory drugs and non-opioid analgesics, in the management of post-operative pain in children. Nevertheless, the PRAC concluded that codeine still has a place in the treatment of acute pain in the paediatric population but given the concerns about its risks, it should only be used when in the management of acute moderate pain which is not considered to be relieved by other analgesics. It was also recommended that it should be used at the lowest effective dose for the shortest period of time.

While acknowledging that uncertainties remain regarding the identification of particular paediatric populations at higher risk and the impact of age on codeine metabolism, the PRAC was of the opinion that neonates, toddlers and young children may be more vulnerable to opioid toxicity. In order to adequately minimise this risk, the PRAC considered that codeine should only be used in children above 12 years of age, since the enzymatic systems responsible for the metabolism of codeine in children older than 12 years of age can be considered comparable to that of adults. In addition, CYP2D6 is subject to extensive polymorphism, with poor metabolisers likely to exhibit lower response to treatment, while extensive and ultra-rapid metabolisers are at risk of serious and fatal adverse events of opioid toxicity. The PRAC noted that performing genotype/phenotype screening of patients before prescribing codeine is unfeasible in practice, therefore, adequate warnings to highlight these risks were recommended, including signs and symptoms of opioid toxicity and estimates of the prevalence of ultra-rapid metabolisers in different populations.

The PRAC noted that the six published cases of opioid toxicity (including three with fatal outcomes) in children taking codeine at recommended doses after tonsillectomy or/and adenoidectomy for obstructive sleep apnoea occurred in children. Three were subsequently found to be either ultra-rapid or extensive metabolisers of codeine and their underlying breathing problems may have made them more sensitive to develop respiratory depression when codeine converts to high levels of morphine in ultra-rapid metabolisers. Therefore, the PRAC considered that in children below 18 years of age that undergo tonsillectomy and/or adenoidectomy for Obstructive Sleep Apnoea Syndrome, the use of codeine should be contraindicated. In addition, the PRAC recommended caution in the specific subpopulation of patients who might already have a compromised airway and require post-operative pain relief and adequate warnings were reflected in the product information.

The PRAC also noted the published case of respiratory depression resulting in death in a breastfed newborn whose mother was a CYP2D6 ultra-rapid metaboliser. It was acknowledged that this was due to the presence of codeine metabolites in breast milk and the PRAC therefore raised concerns regarding the risk of opioid toxicity to the infant, which may be fatal, when the mother is an ultra-rapid metaboliser. To date, at least 44 cases of neonatal respiratory depression in breastfeed infants of codeine-using mother have been published. In view of these data, the PRAC recommended to contraindicate the use of codeine in women during breastfeeding. The use of codeine should also be contraindicated in patients of all ages who are known to be CYP2D6 ultra-rapid metabolisers.

The PRAC also concluded that the available data shows that codeine has a ceiling effect at higher doses, above which there is a marked increase in the incidence of adverse drug reactions and that these are dose dependent. The PRAC therefore considered a paediatric dose range of 0.5 to 1mg/kg to

be appropriate, with accurate dosing based on body weight where feasible, with a duration of use limited to three days.

Having noted all of the above, the PRAC concluded that the benefit-risk balance of codeine-containing products indicated in the management of acute moderate pain in children remains favourable, subject to the agreed indication, contraindications, warnings and other changes to the product information as set out in Annex III to the opinion.

2.7. Communication plan

The PRAC agreed on the following key elements for national communication, which should be considered by MAHs when agreeing a communication strategy with their national competent agency:

- Codeine is a widely used analgesic, which requires the cytochrome P450 enzyme CYP2D6 for conversion morphine. Morphine is responsible for codeine's pharmacological effect.

- There are genetic differences in the expression of the CYP2D6 enzyme, according to racial or ethnic group. These differences determine the extent to which codeine is metabolised. Some individuals are deficient in this enzyme and will obtain no analgesic effect from codeine. Whilst other individuals have more than two copies of the gene for this enzyme and are known as ultra-rapid metabolisers, these individuals are more likely to have side-effects because they convert codeine to morphine more quickly or in greater quantities.

- PRAC has reviewed the benefit-risk of products containing codeine for the relief of pain in children. The reason for this review was some fatal or life-threatening cases of morphine intoxication in children who were found to be ultra-rapid or extensive metabolisers and were receiving codeine for the management of pain after adenoidectomy/tonsillectomy for obstructive sleep apnoea.

- Considering that no tests are available for routine screening of CYP2D6 polymorphism, and therefore the conversion to codeine to morphine may be unpredictable, PRAC recommends a number of risk minimisation measures to ensure that only children for whom benefits are greater than the risks are given codeine for pain relief:
    - Codeine is indicated in children older than 12 years of age for the treatment of acute moderate pain which is not relieved by other analgesics such as paracetamol or ibuprofen alone
    - Codeine is contraindicated in paediatric patients 0 to 18 years of age that undergo tonsillectomy and/or adenoidectomy for Obstructive Sleep Apnoea Syndrome due to an increased risk of developing serious and life-threatening adverse reactions including loss of consciousness and respiratory arrest.
    - Codeine is contraindicated in patients known to be CYP2D6 ultra-rapid metabolisers as the risk of morphine intoxication is extremely high in these patients.
    - Codeine is not recommended for use in children whose breathing might be compromised including children with neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. The symptoms of morphine toxicity may be increased in these settings.

- Due to an increased risk for the breastfeeding child when mother is using codeine and she is an ultra-rapid metaboliser, the use of codeine is contraindicated in women when breastfeeding.

- Codeine should be used at the lowest effective dose for the shortest period of time. This dose may be taken, up to 4 times a day at intervals of not less than 6 hours. Maximum daily dose should not exceed 240 mg. The duration of treatment should be limited to 3 days and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician.

- Clinicians should remain aware that patients may respond differently to codeine. Those caring for patients taking codeine should be advised to seek medical advice if symptoms of toxicity occur.

Symptoms of codeine toxicity include reduced levels of consciousness, lack of appetite, somnolence, constipation, respiratory depression, 'pin-point' pupils, nausea and vomiting.

2.8. Changes to the product information

Regarding Section 4.1, the PRAC considered that codeine-containing products should only be used when other analgesics have failed to relieve the pain. In order to minimise the risk of opioid toxicity, based on the reviewed data and the established knowledge of the maturation of the codeine metabolising enzymes, it was also considered it appropriated to restrict the use of codeine to children older than 12 years, for whom the system is considered to be similar to that of adults. Regarding pain intensity, the PRAC considered that the available data provides strong evidence demonstrating that the analgesic effect of codeine is limited in severe pain, even at high doses. The indication was therefore restricted to acute moderate pain, which is considered sufficiently inclusive to cover the different types of acute pain for which codeine has shown efficacy, but only when not relieved by other analgesics. In conclusion, the PRAC recommended the indication in patients older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen alone.

Regarding Section 4.2, the PRAC reviewed the duration of use of codeine-containing products and decided that it was necessary, based on the available data, to limit the use of codeine to the lowest effective dose for the shortest period of time and that the maximum duration of use should be restricted to 3 days as a risk minimisation measure. This time period was considered a reasonable time to get an effect, bearing in mind that 7% of Caucasians will not respond to treatment due to a deficiency in CYP2D6. A statement was also added advising that a physician should be consulted if no effective pain relief is achieved. The PRAC also reviewed the available pharmacokinetic data to determine the interval for administration. While the data supports an analgesic duration of effect between 4 and 6 hours, the PRAC considered a 6-hours interval to be appropriate since this longer interval among doses may mitigate the life-threatening reactions derived from morphine toxic levels in ultra-rapid metabolisers. With regard to the maximum daily dose, taking into account the proposed paediatric dose range of 30 to 60 mg body weight (based on 0.5 to 1mg/kg), the PRAC considered that the available data supports a maximum daily dose of 240 mg for codeine-only products. However, for combination products, the PRAC acknowledged that this maximum limit needs to be adjusted for each individual dose, due to the lower codeine content.

Regarding Section 4.3, the PRAC was of the view that the fatal cases identified in children with sleep apnoea syndrome after tonsillectomy or adenoidectomy warrant a contraindication in this population, especially since the respiratory depression caused by morphine intoxication may be more severe in these children. Similarly, fatal cases of newborns being breastfed by ultra-rapid metaboliser women have been published. A warning was considered to be insufficient, as women will not normally know if they are ultra-rapid metabolisers and a contraindication in women during breastfeeding was therefore recommended, together with a statement in Section 4.6. Finally, the PRAC also considered it appropriate to contraindicate the use of codeine in patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.

The PRAC was of the view that information on CYP2D6 polymorphisms, including a tabular presentation of prevalence, should be provided to prescribers in Section 4.4, since prevalence according to population varies broadly. Based on the available data, the PRAC also considered it highly relevant to include extensive metabolisers, alongside ultra-rapid metabolisers, as one of the cases of severe codeine intoxication in the published literature that triggered this review was observed in an extensive metaboliser. Furthermore, in the majority of the reported adverse drug reaction cases, the lack of information on CYP2D6 status does not allow any robust conclusions on the risk of harm in EMs. Finally, a statement regarding the analgesic properties of codeine was added in Section 5.1.

The package leaflet was revised accordingly.

3. Conclusion and grounds for the recommendation

Whereas,

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, for codeine-containing products indicated in the management of pain in children (see Annex I).
- The PRAC considered the totality of the data available for codeine-containing products indicated in the management of pain in children in relation to the risk of opioid toxicity. This included the MAH responses and published literature data which became available since the initial granting of the marketing authorisations.
- The PRAC concluded that the available data indicates that codeine remains an effective analgesic for the treatment of acute moderate pain which is not considered to be relieved by other analgesics. However, the PRAC also considered that its use can be associated with serious adverse events of opioid toxicity, in particular in the paediatric population below 12 years of age.
- The PRAC considered that serious adverse events of opioid toxicity are of particular concern in paediatric patients undergoing tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome and in patients with compromised respiratory function.
- The PRAC also determined that polymorphisms in the cytochrome P450 CYP2D6 system impact the metabolism of codeine, which can result in serious adverse events of opioid toxicity in ultra-rapid or extensive codeine metabolisers. The PRAC considered this risk to be of relevance to breast-fed infants whose mothers are ultra-rapid metabolisers.
- The PRAC therefore considered that in view of the available data and in order to maintain a favourable benefit-risk balance, codeine-containing products indicated in the management of pain should only be indicated in children above 12 years of age and contraindicated in paediatric patients below 18 years of age undergoing tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome as well as in women during breast-feeding and in patients known to be CYP2D6 ultra-rapid metabolisers. Moreover, codeine-containing products should be used at the lowest dose for the shortest duration possible.

The PRAC, as a consequence, concluded that subject to the agreed indication, contraindications, restrictions, warnings and other changes to the product information, the benefit-risk balance for codeine-containing products indicated in the management of acute moderate pain in children above 12 years of age remains favourable.

Therefore, in accordance with Articles 31 and 32 of Directive 2001/83/EC, the PRAC recommends the variation of the marketing authorisations for all medicinal products referred to in Annex I and for which the amendments to the product information are set out in Annex III of the recommendation. The PRAC also considered that it may be relevant to consider the need to extrapolate this recommendation to other codeine indications.

A divergent position is appended to the Recommendation.

Appendix 1

Divergent positions dated 13 June 2013

Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-31/1342

Codeine-containing medicinal products indicated for the treatment of pain in children

Divergent statement

The following member of PRAC did not agree with the PRAC's Recommendation on the Article 31 referral resulting from pharmacovigilance data for codeine-containing medicinal products used for pain in children based on the following reasons:

- I support the PRAC conclusion on the benefit-risk of codeine in the treatment of pain in children and the product information wording as adopted by PRAC, with the exception of the contraindication in breastfeeding. While I agree that there is an unpredictable risk of morphine toxicity for the infant depending on mother's metabolism of codeine, this risk depends on doses in milk and length of treatment. Milk levels of codeine and morphine are low, also oral bioavailability of morphine is quite low, however due to prolonged morphine plasma clearance in very young infants their plasma morphine levels increase gradually during prolonged treatment of the mother. Simultaneously the signs of morphine toxicity can appear and worsen gradually. After short-term treatment no important risk can manifest, therefore I consider that the breastfeeding contraindication should be restricted only to treatment longer than 3 days. This is also in line with expert recommendations (e.g. Madadi et al. in Guidelines for maternal codeine use during breastfeeding – CNS depression in the infant appears to worse after 4 days). One or few doses of codeine could be sufficient in the treatment of acute pain in some cases and such a short-term treatment does not raise any significant risk for the breastfed infant.

However even with minimal probability of any risk during short-term therapy the product information should describe the possible signs of morphine toxicity (increased sleepiness, limpness, feeding and breathing difficulties) and recommendation to stop immediately the treatment and contact the physician in case any of these signs appear.

PRAC member expressing a divergent position:

Eva Jirsovà (CZ)	13 June 2013	Signature: ……

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 March 2015
EMA/235820/2015
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Codeine containing medicinal products for the treatment of cough and/or cold in paediatric patients

International non-proprietary name: codeine

Procedure number: EMEA/H/A-31/1394

Note

Assessment report as adopted by the PRAC and considered by the CMDh with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Background information on the procedure

In 2012 - 2013, the Pharmacovigilance Risk Assessment Committee (PRAC) reviewed the benefit-risk of products containing codeine for the relief of pain in children (Referral procedure EMEA/H/A-31/1342[1]). The reason for this review were concerns regarding opioid toxicity and the lack of consistent risk minimisation measures, raised following cases described in the literature of fatal or life-threatening respiratory depression, when codeine was given to children after adenoidectomy/tonsillectomy for obstructive sleep apnoea. A number of the children were subsequently found to be ultra-rapid or extensive codeine-to morphine metabolisers.

In June 2013, PRAC recommended the following risk minimisation measures to ensure that only children for whom benefits are greater than the risks are given codeine for pain relief:

- codeine is only indicated in children older than 12 years of age for the treatment of acute moderate pain which is not relieved by other analgesics such as paracetamol or ibuprofen alone.
- codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine;
- Codeine is contraindicated in paediatric patients 0 to 18 years of age that undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome due to an increased risk of developing serious and life-threatening adverse reactions including loss of consciousness and respiratory arrest.
- Codeine is contraindicated in patients of any age known to be CYP2D6 ultra-rapid metabolisers as the risk of morphine intoxication is extremely high in these patients.
- Codeine is contraindicated in women during breastfeeding, as if the mother is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal.
- Codeine is not recommended for use in children whose breathing might be compromised including children with neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. The symptoms of morphine toxicity may be increased in these settings.

As the above risk minimisation measures could also be applicable to the approved indication of codeine for cough and/or cold, on 02 April 2014, the German National Competent Authority (BfArM) initiated a referral under Article 31 of Directive 2001/83/EC to review the benefit-risk balance of codeine in the treatment of cough and/or cold in paediatric patients (hereafter refer as “children”).

The PRAC was requested to give its opinion on whether the marketing authorisations for codeine-containing medicinal products indicated for cough and/or cold in children, should be maintained, varied, suspended or revoked.

After reviewing all the available data to address the concerns discussed, the PRAC adopted its recommendation on 12 March 2015.

[1] Article 31 pharmacovigilance referral for codeine used for mangement of pain in paediatric patients (EMA/H/A-31/1342) http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Codeine-containing_medicines/human_referral_prac_000008.jsp&mid=WC0b01ac05805c516f

As the request resulted from the evaluation of data from pharmacovigilance activities concerning products only approved nationally (including via the mutual recognition and decentralised procedures), the PRAC recommendation is forwarded to the Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMDh) for a position/agreement to be reached.

2. Scientific discussion

2.1. Introduction

Codeine, also known as methylmorphine, binds to μ-opioid receptors to produce analgesia and euphoria, as well as respiratory depression, miosis, and reduced gastric motility[2] (Buck ML, 2004). Apart from its use as an analgesic for relief of pain, it is also used for the symptomatic treatment of cough and/or cold.

Cough is one of the most common symptoms in children worldwide[3] (Smith S et al, 2008). In most children, acute cough is due to viral upper respiratory tract infection (URTI), i.e., the common cold[4] (De Blasio F et al, 2012).

Numerous preparations containing codeine are available for the symptomatic treatment of cough and/or cold for children in the European Union. The preparations may contain codeine as a single agent or in combination with other active substances.

Codeine suppresses the cough reflex through a direct effect on the cough centre in the medulla. However, there is little clinical data in the medical literature to support the efficacy of codeine as an antitussive as current evidence does not find codeine to be more effective than placebo for acute cough in children[5] (Schroeder and Fahey, 2002).

Codeine is converted into morphine in the body by cytochrome P450 2D6 (CYP2D6), an enzyme which shows genetic polymorphism. It has been established that some patients who are 'CYP2D6 ultra-rapid metabolisers' convert codeine to morphine at a faster than normal rate. This results in high levels of morphine in their blood that can lead to toxic effects such as breathing difficulties. There have been a number reports of serious adverse events in children prescribed codeine, some of which were cases of fatal or life-threatening respiratory depression. As mentioned above, the PRAC has issued a recommendation in 2013 for risk minimisation measures for when codeine is used for relief of pain in children.

The present review concerns the use of codeine in paediatric patients for the cough and/or cold indications as triggered by the German National Competent Authority (BfArM) due to the applicability of the above risk measures also to these indications.

All codeine containing medicinal products approved for the treatment of cough and/or cold in the paediatric population, including single and combination products authorised in the European Union were included in this review.

In April 2014, PRAC agreed a list of questions to be addressed by the marketing authorisation holders (MAHs) of codeine-containing medicinal products used for treatment of cough and/or cold in children.

[2] Buck, M.L., 'Therapeutic Uses of Codeine in Pediatric Patients' Pediatric Pharmacotherapy, 2004;10(4).
[3] Smith S., Schroeder K., Fahey T., 'Over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings (Review)', Cochrane Database Syst, Rev 2008.
[4] De Blasio F., Dicpinigaitis P.V., Rubin B.K., De Danieli G., Lanata L., Zanasi A., 'An observational study on cough in children: epidemiology, impact on quality of sleep and treatment outcome', Cough, 2012;8(1):1.
[5] Schroeder K., Fahey T., 'Should we advise parents to administer over the counter cough medicines for acute cough? Systematic review of randomised controlled trials', Arch Dis Child, 2002 Mar;86(3):170-5.

2.2. Clinical aspects

Cough is a reflex response to mechanical, chemical, or inflammatory irritation of the tracheobronchial tree. Cough serves as a physiologic function to clear airways of obstructive or irritating material or to warn of noxious substances in inspired air.

Acute cough is defined as cough lasting less than 3 weeks whereas chronic cough lasts more than 8 weeks (or more than 4 weeks, depending on the definition). The majority of children with acute cough have a viral respiratory tract infection and for the majority of children acute cough resolves within 14 days and - more rarely - within 3-4 weeks. Rarer causes of acute cough in children include seasonal allergic rhinitis, inhaled foreign body or first presentation of a chronic disease[6,7,8](Brodlie M et al 2012, Irwin RS et al 2006, Shields MD et al 2008).

The aetiology of chronic cough in children usually comprises underlying diagnoses such as asthma, allergic rhinitis, persistent endobronchial infection, recurrent aspiration, interstitial lung disease, tuberculosis or cardiac diseases. Most chronic coughs in childhood are not due to the same conditions as occur in adults; the 'big three' causes of adult chronic cough are noted to be cough variant asthma, postnasal drip and gastro-oesophageal reflux. The use of adult-based cough algorithms is unsuitable for application in children[8] (Shields MD et al 2008). Chronic cough in children should be managed by making an accurate underlying diagnosis and then applying specific treatment for this condition[8,9] (Shields MD et al 2008, ACCP evidence-based clinical practice guidelines 2006).

The frequency of acute upper respiratory tract infections (URTIs) is also age-related and differs between adults and children. Studies from the 1940s to the 1960s have shown that children have 5 to 8 acute respiratory infection episodes per year, while in more recent studies children aged < 5 years have 3.8 to 5 infections per year and adults have only 2[9] (ACCP evidence-based clinical practice guidelines 2006).

In conclusion, acute cough in children is frequent, usually caused by viral infection and self-limiting whereas in the case of chronic cough, treatment should be directed at the underlying disease[10,11] (American Academy of Paediatrics Committee on Drugs 1997, American Academy of Paediatrics, AAP publications retired or reaffirmed 2006).

In its assessment, the PRAC considered the data available from different sources: clinical trials, observational studies, meta-analyses, post-marketing data and further published data on the use of codeine containing products in children for treatment of cough and/or cold.

The PRAC also considered data from the European Pharmacovigilance database (Eudravigilance), a drug utilisation study of the patterns of prescription of codeine. Moreover the PRAC consulted European healthcare professional organisations and the Paediatric Committee (PDCO).

A summary and discussion of relevant data is presented hereafter.

[6] Brodlie M., Graham C., McKean M.C., 'Childhood cough', BMJ, 2012;344:e1177.

[7] Irwin R.S., Baumann M.H., Bolser D.C. et al. 'Diagnosis and management of cough executive summary: Accp evidence-based clinical practice guidelines', Chest, 2006;129(1_suppl):1S-23S.

[8] Shields M.D., Bush A., Everard M.L., McKenzie S., Primhak R., 'Recommendations for the assessment and management of cough in children', Thorax, 2008;63(Suppl 3):iii1-iii15.

[9] American College of Chest Physicians evidence-based clinical practice guidelines 2006

[10] American Academy of Pediatrics Committee on Drugs 'Use of codeine- and dextromethorphan-containing cough remedies in children', Pediatrics 1997;99:918-20.

[11] American Academy of Pediatrics. AAP Publications Retired or Reaffirmed, October 2006. Pediatrics 2007;119(2):405.

2.2.1. Pharmacokinetics, Pharmacogenomics and Pharmacodynamics

During the Article 31 referral review on codeine containing medicinal products indicated in the management of pain in children an extensive discussion took place regarding the pharmacokinetics (PK), pharmacogenomics and pharmacodynamics (PD) of codeine metabolism. A brief summary is presented hereafter on aspects relevant to codeine containing medicinal products indicated for cough and/or cold in paediatric population.

O-demethylation of codeine into morphine is mediated by the enzyme CYP2D6[12] (Kirchheiner et al, 2007). It has been established that CYP2D6 is subject to extensive polymorphism resulting from more than 100 different known allelic variants. Individuals are commonly grouped in 4 different phenotypes: poor metaboliser (PM), intermediate metaboliser (IM), extensive metaboliser (EM) and ultra-rapid metaboliser (UM). Regarding UMs, the overall prevalence in Caucasians is up to 10% but ranges from low in northern Europe (1-2% in Finland, Denmark, Norway and Sweden), Central Europe, North America (4-5%) and Asia (0.5-2.5%), to significantly higher in the Mediterranean countries (7-12% in Portugal, Spain, Greece and Italy), Saudi Arabia (21%) and Ethiopia (29%).

The vast majority of PK and PD data for codeine have been obtained from investigations in adults and the data mainly focus on codeine's analgesic properties. PK, PD data and clinical evidence that explain how CYP2D6 phenotypes relate to variable efficacy in cough control after codeine intake are lacking.

There have been no direct pharmacogenomics studies identified in the published literature related to codeine administration for cough and/or cold in the paediatric population. It is believed that the antitussive action of codeine works via stimulation of μ-opioid receptors[13] (McDonald, 2005). μ-Opioid receptors are found within the cough centres of the brain and therefore, it is thought that opioids exert their antitussive effects via a central action[14] (Gibson et al, 2011).

Bibliographic literature indicates that codeine has a 200-fold weaker affinity for μ-opioid receptors than morphine[15] (Crews et al, 2014). Therefore, codeine antitussive properties (similar to codeine analgesic properties) may be closely related to CYP2D6 and will vary depending on its conversion to morphine.

The phenotypic variability refer above is translated into a wide spectrum of metabolic capacity in terms of the ability to metabolise codeine. Hence, in terms of efficacy, weaker antitussive properties can be expected in poor metabolisers because less codeine would be converted into morphine; whereas extensive and ultra-rapid metabolisers would have the opposite effect which may result in potentially toxic concentration of morphine even when low doses of codeine are given.

The unpredictable and variable metabolism of codeine in children, as governed by CYP2D6 polymorphism may cause some children to exhibit codeine toxicity even within the recommended doses. Therefore, this continues to represent a variable safety risk across all paediatric age groups.

The PRAC recommended that information regarding ultra-metabolisers CYP2D6 need to be reflected in the product information for all codeine containing medicinal products approved for cough and/or cold in children in line with the PRAC recommendation for the medicinal products of codeine indicated for pain relief, in the same population.

[12] Kirchheiner J., Schmidt H., Tzetkov M. et al. 'Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolisers due to CYP2D6 duplication', Pharmacogenomics, J 2007;7:257–265.

[13] McDonald J., Lambert D.G.,'Opioid receptors. Continuing Education in Anaesthesia, Critical Care & Pain', 2005;5(1):22-25.

[14] Gibson P.G. et al. 'Cough pharmacotherapy: current and future status. Expert Opin. Pharmacother', 2011;12(11). (P11-09653).

[15] Crews K.R., Gaedigk A., Dunnenberger H.M., et al. 'Clinical Pharmacogenetics Implementation Consortium (CPIC). Guidelines for Codeine Therapy in the Context of Cytochrome P450 2D6 (CYP2D6) Genotype', Clin Pharmacol Ther, 2012; 91:321-326.

2.2.2. Clinical Efficacy

Codeine suppresses the cough reflex through a direct effect on the cough centre in the medulla. However, there is little clinical data in the medical literature to support the efficacy of codeine in the symptomatic treatment of cough and/or cold as current evidence does not find codeine to be more effective than placebo for acute cough in children[16] (Schroeder and Fahey, 2002).

Published studies

In total, only 4 published studies investigating the use of codeine-containing medicines for the treatment of cough and/or cold in children could be identified. There was also a Cochrane review in 2012 which identified two studies on the use of codeine in cough and/or cold in adults and only one in children.

Two older studies, which do not meet today's guidelines, did not include a placebo group. Firstly, Kelly and colleagues[17] (1963) conducted a single blind study in children aged 8 months to 17 years with acute cough due to respiratory infection. 26 children received codeine (8 mg/16 mg four times a day for productive/unproductive cough), 27 received pholcodine (5 mg/10 mg) and 8 received both treatments on a crossover basis. Treatment duration was approximately 5 days. 96 % of patients treated with pholcodine and 93 % of patients of patients treated with codeine had excellent or good results, but the duration of effect was greater in the pholcodine group than in the codeine group (4 hours versus 3 hours). No adverse drug reactions were observed in the pholcodine group while 8 of 26 patients in the codeine group complained of mild constipation.

Secondly, a randomised, single-blind trial included 217 children aged 6 –12 years with acute cough and compared the efficacy and palatability of two combination products given for 3 days. Patients had acute cough due to upper respiratory or chest infection with median symptom duration of 3 days. Each patient received either a product containing paracetamol 150 mg, pholcodine 5 mg and phenylpropanolamine 12.5 mg four times daily, or a product containing triprolidine hydrochloride 1.875 mg, pseudoephedrine hydrochloride 45 mg and codeine phosphate 15 mg three times daily. Both products showed highly significant improvements for productive cough and sore throat. Side effects were significantly less frequent in the pholcodine-containing product, and drowsiness was observed significantly more frequently with the codeine-containing product. Analysis of palatability showed numerical superiority for the pholcodine-containing product[18] (Jaffe G et al, 1983).

The PRAC also noted one observational study evaluating the epidemiology and impact of cough on quality of sleep and children's activities, and the outcome of cough with antitussive treatments in paediatric routine clinical practice. A total of 433 children aged 1 month to 14 years (mean age 6.1 years (SD 3.6 - median 5.2 years)) with acute cough (onset ≤ 3 weeks) associated with URTI were enrolled[4] (De Blasio F et al, 2012).

In a subset of 241 children who were either treated with antitussive medicines (levodropropizine n=101, central antitussives (cloperastine n = 51 or codeine n=9) or received no treatment (n = 80), the outcome of cough after 6 days was analysed in terms of resolution, improvement, no change, or worsening. Both levodropropizine and central drugs reduced cough intensity and frequency. However, percentage of cough resolution was significantly higher with levodropropizine than with central

[16] Schroeder K., Fahey T., 'Should we advise parents to administer over the counter cough medicines for acute cough? Systematic review of randomised controlled trials', Arch Dis Child, 2002 Mar;86(3):170-5.
[17] Kelly D.A., 'Comparative clinical test of pholcodine with codeine as control'. Northwest Med 1963;62:871-874
[18] Jaffe G., Grimshaw J.J., 'Randomized single-blind trial in general practice comparing comparing the efficacy and palatability of two cough linctus preparations, 'Pholcodix' and 'Actifed' compound, in children with acute cough', Curr Med Res Opin, 1983;8:594-599.

antitussives (47% vs. 28% respectively, p = 0.0012). Improvement was observed in 40% of patients receiving levodropropizine *vs.* 53 % for central antitussives and no change/worsening was reported in 3% receiving levodropropizine *vs*. 18% for central antitussives. Of note 20% of patients receiving no therapy reported resolution of cough, while 55% reported improvement of their symptoms and 25% no change/worsened. Multivariate analysis showed a statistically significant difference of cough improvement with levodropropizine *vs.* central antitussives or no therapy. No information on adverse drug reactions was presented in this publication.

There was a double-blind, randomised controlled trial (RCT) that compared the effects of dextromethorphan, codeine and placebo on 57 patients aged between 18 months to 12 years presenting with acute cough of less than 2 weeks duration. Cough and composite symptom scores, based on symptom severity at bedtime, were obtained using parent questionnaires. Mean cough and composite symptom scores were found to decrease significantly in each of the 3 groups ($p<0.0002$). However, regression analysis showed that neither dextromethorphan ($p = 0.41$) nor codeine ($p=0.70$) was significantly better than placebo in relieving night time symptoms[19] (Taylor et al, 1993).

In 2012, a Cochrane review of non-prescription/over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings[20] (Smith SM et al, 2012) identified two randomised controlled trials where codeine was tested in adults[21,22] (Eccles R et al, 1992; Freestone C 1997). In these two studies, codeine was found to be no more effective than placebo. In the review published by the Cochrane Collaboration (addressing the efficacy and safety of OTC cough and/or cold medications in the ambulatory setting), only one trial[20] (Taylor et al, 1993, discussed above) on codeine was identified in children.

Conclusions on efficacy

Overall, there is limited evidence in the medical literature to support the use of codeine in cough and/or cold and a clear paucity of clinical trials investigating the antitussive efficacy of codeine in children.

In total, only 4 published studies investigating the use of codeine-containing medicines for the treatment of cough in children could be identified along with a systematic review published by the Cochrane Collaboration.

Efficacy data is therefore limited, with no recent and well-established, controlled scientific studies to clearly support the benefit of codeine in the approved indications for cough and/or cold for the paediatric population.

2.2.3. Clinical safety

The use of opioids in children entails a known risk of central respiratory depression. The safety profile of codeine raises greater concerns as codeine is metabolised to morphine at an unpredictable rate.

[19] Taylor J.A., Novack A.H., Almquist J.R., Rogers J.E., 'Efficacy of cough suppressants in children' J Pediatr 1993;122:799-802.
[20] Smith S.M., Schroeder K., Fahey T., 'Over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings', Cochrane Database Syst Rev, 2012;8:CD001831.
[21] Eccles R., Morris S., Jawad M.S., 'Lack of effect of codeine in the treatment of cough associated with acute upper respiratory tract infection', J Clin Pharm Ther, 1992;17:175-80.
[22] Freestone C., Eccles R., 'Assessment of the antitussive efficacy of codeine in cough associated with common cold', J Pharm Pharmacol, 1997;49(10):1045-9.

The most common adverse reactions to codeine (independently of the indication of its use) include drowsiness, light-headedness, dizziness, sedation, shortness of breath, nausea, vomiting and sweating. Serious adverse reactions include respiratory depression and, to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

Post marketing data

A review of spontaneous case reports revealed 9 fatal cases and 41 serious cases associated with codeine use in the paediatric population. In many of these cases, the indication of use for codeine is not clear. Out of the 9 fatal cases, 3 cases were reported in the setting of codeine being used for cough or respiratory infection. Out of the 41 serious cases, there were 5 cases in which the indication of use has been reported as cough or upper respiratory tract infection or peri-tonsillar abscess. These five cases involved 1 case of apnoea, 3 cases of skin reactions and 1 case of paracetamol intoxication/acute liver failure.

The fatal and serious cases reviewed highlight the risk of morphine toxicity in the subpopulation of patients with compromised respiratory function, (e.g. post-operatively after tonsillectomy and/or adenoidectomy) and also indicate a higher reporting of opioid toxicity and respiratory depression in young children (<12 years) regardless of the indication of use of codeine.

Nonetheless, the under-reporting issue of suspected adverse reactions for all non-prescription/over-the-counter (OTC) medicines and particularly for long-established products is recognised. Therefore the evaluation of a safety signal in the paediatric population based on these cases is difficult.

Literature data

An overview of all published cases is presented in table 1. below.

Table 1. Summary tabulation of case reports of codeine intoxication in children related to the treatment of cough and respiratory infection

Author (year)	Age	Codeine dose / concomitant medication	Indication	Adverse reactions	Outcome	Comments
Magnani (1999)	29 d	2 doses of 2 mg codeine + 6 mg pseudoephedrine + 0.4 mg chlorpheniramine + 5 % alcohol within 6 hours (1.26 mg/kg/d of codeine)	Cough, respiratory infection	Apnoea 2 hours after second dose	Fatal	Post mortem heart blood: 0.34µg/ml free codeine, 0.48 µg/ml total codeine
Lee (2004)	3 months	5 mg codeine + 2.5 mg ephedrine + 1 mg dexchlorpheniramine + 50 mg ammonium 3 times daily (2 mg/kg/d) / Ceftibuten 50 mg/d, L-chlorpheniramine 3 x 1mg/d	Persistent cough	Cyanosis, dusky complexion and mottled Skin, with poor response to external stimuli on second day	Full recovery	
Hermans-Clausen (2009), Ferreiros (2009)	3 years (twin 1)	About 12.3 mg to 23.4 mg of codeine per day for 6 days (0.9 – 1,7 mg/kg/d) / Acetaminophen, ibuprofen, ivy leaf extract	Persistent cough, fever, URTI	Apnoea, vomiting	Full recovery	Serum concentration: 174.0 ng/ml codeine, 25.6 ng/ml morphine, CYP2D6 extensive metaboliser genotype. Medication error
Hermans-Clausen (2009), Ferreiros (2009)	3 years (twin 2)	About 12.3 mg to 23.4 mg of codeine per day for 6 daysd (0.9 – 1.7 mg/kg/d) / Acetaminophen, ibuprofen, ivy leaf extract	Persistent cough, fever, URTI	Apnoea, vomiting	Fatal	Serum concentration: 463.3 ng/ml codeine, 138.7 ng/ml morphine, CYP2D6 extensive metaboliser

Author (year)	Age	Codeine dose / concomitant medication	Indication	Adverse reactions	Outcome	Comments
						genotype. Medication error
Tong (2001)	17 days	6mg of codeine three times daily (6.6 mg/kg/d) / Chlorpheniramine 0.5 mg three times daily	Cough	Cyanotic episodes 2, 3 and 6 hours after the third codeine administration	Full recovery	Codeine blood level: 0.24 µg/ml 9 hours after last dose.
Friedrichsdorf (2013)	6 years	3 doses of 10 to 20 mg codeine with guaifensin within 12 hours (0.22-0.44 mg/kg/d) / Azithromycin	Severe cough and respiratory infection	Death during sleep 13 hours after last dose	Fatal	0.08 mg/l free codeine, 0.17 mg/l total codeine, 0.08 mg/l total morphine, obesity (44.9 kg, BMI 26.6). Correct dose despite medication error.
Wilkes (1976)	3 months	2 doses of 10 mg codeine with pseudoephedrine and triprolidine (6.6 mg/kg/d)	URTI	Sleepiness, heavy breathing, miosis, apnea following 2 doses within 24 hours	Full recovery	Medication error
Riedler (1988)	7 weeks	2 doses of 5 mg codeine with dimethylaminophenazone, diallylbarbiturate and phenylcyclohexylacetate within 12 hours	URTI	Coma, hypertension, opistothotonus, miosis and respiratory depression 2 hours after the second dose. Apnea 10 hours after the second dose	Full recovery	Medication error
Rumler et al (1963)	4 months	At least 20 mg of codeine per day for 2 days (3.9 mg/kg/d)	URTI	Gray and pale complexion, restlessness, opisthotonus, miosis, obstipation	Full recovery	Iatrogenic overdose
Rumler et al (1963)	4 weeks	30 mg of codeine within 8 hours (9.7 mg/kg)	URTI	Difficulty breathing, screaming, severe cyanosis, tonic stiffness of arms and legs, opisthotonus, trism, bradycardia, obstipation, miosis	Full recovery	Prescribing error, medication error by parents.
Rumler et al (1963)	9 months	At least 12 mg of codeine per day for 10 days (1.4 mg/kg/d)	Pertussis	Cyanosis , tonic clonic convulsions, subileus, death a few hours after admission	Fatal	Medication error by parents
Rumler et al (1963)	3 months	2 suppositories containing in total 10 mg codeine, 5 mg theobromine and 5 mg atropa belladonna extract within a short period of time (2 mg/kg)	URTI, bronchitis	Facial edema, moderate cyanosis, subileus, tonic convulsions,	Full recovery	Medication error by parents
Rumler et al (1963)	11 weeks	About 20 mg of codeine within 3 days (1.1 mg/kg/d)	URTI,	Gray pale complexion, generalized edema, shallow breathing, miosis, obstipation, limp	Full recovery	Iatrogenic overdose
Rumler et al (1963)	5 months	1 suppository for adults containing 30 mg codeine, 400 mg aminophenazone , 75 mg theobromine and 25 mg atropa belladonna extract (4.1 mg/kg)	URTI,	Generalized hyperaemia, somnolence, tachycardia, tonic convulsions, mydriasis, obstipation	Full recovery	Off-label use/Medication error by parents

In total, fourteen reports of codeine intoxication in children related to the treatment of cough and respiratory infection were identified in the published literature. A review of these cases indicated that, four cases had a fatal outcome. The remaining cases were all life-threatening but resulted in full recovery. The children's age ranged from 17 days to 6 years.

The dose of codeine given varied from 0.22 mg/kg/day to 6.6 mg/kg/day. Assuming a recommended maximum daily dose of 1 mg/kg/day[10] (American Academy of Paediatrics Committee on Drugs 1997), one patient was given a dose within the recommended dosing range and 13 of the patients were overdosed. The patient who had received codeine within the recommended antitussive dosing range (0.22-0.44 mg/kg/d) died during their sleep thirteen hours after the last dose[23] (Friedrichsdorf et al, 2013).

The majority (8 out of 13) of the overdoses including the 3 fatal cases however were only in the range of ≤ 2 mg/kg per day or per single dose corresponding to only 2 times the maximum recommended daily dose and a dose generally considered as not life-threatening[24] (von Muhlendahl et al, 1976).

The CYP2D6 genotype was known in two cases. Both children were extensive metabolisers[25] (Hermanns-Clausen et al, 2009).

Combination products containing other centrally acting drugs (antihistamine, barbiturates) were reported in four cases.

EudraVigilance data

Case reports with adverse drug reactions that could be related to opiate toxicity in paediatric patients were selected (cut-off 31 July 2014). In total 50 case reports were identified of which 31 cases were in those < 6 years (including 4 fatal cases), 7 cases were in those ≥ 6 and <12 years (including 1 fatal case) and 12 cases in those ≥ 12 and <18 years (including 1 fatal case).

Overall, the majority (38/50) of the cases were in patients < 12 years of age and 6 were fatal cases. The additional fatal case occurred in a patient aged between ≥ 12 and <18 years.

Of the 7 fatal case reports [ages 4 mths, 2 years, 3 years, 5 years (n=2 but likely duplicates), 6 years, 15 years] one is sufficiently well documented to suggest opiate toxicity despite dosing within the recommended range. In one other case an overdose due to medication error cannot be excluded. The remaining cases (including 1 duplicate) provide insufficient information for a causality assessment or are suggestive of alternative causes of death. Dose and duration of codeine treatment were reported only in the first two cases mentioned.

The System Organ Class for which the highest numbers of cases were reported were general disorders and administration site conditions (15), injury, poisoning and procedural complications (13), nervous system disorders (27) and respiratory, thoracic and mediastinal disorders (19). The most frequently reported reactions (MedDRA preferred term, > 3 case reports) were vomiting (7 reports), accidental overdose (4), medication error (4), toxicity to various agents (4), convulsion (7), lethargy (4), somnolence (5), apnoea (5) and dyspnoea (5).

[23] Friedrichsdorf S.J., Nugent A.P., & Strobl A.Q., 'Codeine-associated pediatric deaths despite using recommended dosing guidelines: three case reports', J Opioid Manag, 2013;9(2):151-155.
[24] von Muehlendahl KE, Scherf-Rahne B, Krienke EG, et al. Codeine intoxication in childhood. *Lancet* 1976;7:303-305.
[25] Hermanns-Clausen M. ,Weinmann W., et al. 'Drug dosing error with drops: severe clinical course of codeine intoxication in twins', Eur J Pediatr, 2009;168(7):819-24.

Codeine misuse and dependence in adolescents

In adolescents, the additional risk of codeine dependence and abuse has been identified. There have been reports both in the published literature and also from spontaneous reporting that codeine containing products are used as substances of abuse either on their own or as substitutes for conventionally abused drugs, especially in adolescents.

Several MAHs searched their safety databases and performed literature searches, with a particular focus on the potential for codeine abuse and dependence in the 12-18 year age group.

Haifeng and colleagues[26] (2011) reported that chronic abuse of codeine containing cough syrups can induce physical and psychological dependence. The results suggested that chronic abuse of those syrups may cause serious damage to the brain. Chronic abuse of codeine containing cough syrups could lead to chronic overdose and opioid toxicity.

Several authors have also reported that codeine-containing products are used as substances of abuse either on their own or as substitutes for conventionally abused drugs such as heroin, amphetamine and cocaine, especially in adolescents[27,28,29](Lao YZ et al 2010, Mattoo SK et al 1997, Yang and Yuan 2008).

Reed and colleagues[30] (2011) have stated that recreational use of over-the-counter codeine-containing products by young people (younger than 16 years), although likely to be spasmodic, often occurs in combination with other drugs or alcohol leading to potentially greater adverse effects.

The misuse of OTC cough and/or cold medications among adolescents was also examined with data from the 2006 National Survey on Drug Use and Health (USA)[31] (Ford JA, 2009). Findings from this research indicate that a small percentage (nearly 4%) of adolescents report lifetime misuse of OTC medications. The analysis indicates that risk for misuse increases with age, as respondents between ages 13 and 17 are more likely to report misuse than adolescents of 12 year old.

Codeine in breastfeeding mothers

Over the recent years there have been reports of infant deaths due to high levels of morphine in breast milk because their mothers were ultra-rapid metabolisers of codeine[32] (Watt et al, 2013). This evidence indicates a significant risk to the infants when breastfeeding mothers are exposed to codeine regardless of the indication.

One case reported in a MAH's database involved a 1-year-old female child who experienced foetal arrhythmia, hepatotoxicity, jaundice, developmental delay and dependence after exposure of codeine phosphate/paracetamol and paracetamol via transplacental route. The female infant was born to a

[26] Haifeng H., et al. 'Decreased striatal dopamine transporters in codeine-containing cough syrup abusers' Drug and Alcohol Dependence, 2011;118:148-151.
[27] Lao Y.Z., Jiang Z.Y., Tong Z.S., Pang Z.T., Xu J.X., 'Clinical features and defense styles in patients with cough medicine abuse', Med J Chinese People's Health, 2010; 22:272–274.
[28] Mattoo S.K., Basu D., Sharma A., Balaji M., Malhotra A., 'Abuse of codeine containing cough syrups: a report from India', Addiction, 1997; 92:1783–1787.
[29] Yang Y., Yuan Q.Y., 'Investigation and analysis on personalities of male—codeine phosphate addicts by MMPI', Chinese J Drug Abuse Prev Treat, 2008;14:143–145.
[30] Reed K., Bond A., Witton J., Cornish R., Hickman M., Strang J., 'The changing use of prescribed benzodiazepines and z-drugs and of over-the-counter codeine-containing products in England: a structured review of published English and international evidence and available data to inform consideration of the extent of dependence and harm', The National Addiction Centre, Kings College London and School of Social and Community Medicine University of Bristol, University of Bristol, 2011.
[31] Ford J.A., 'Misuse of Over-the-Counter Cough or Cold Medications Among Adolescents: Prevalence and Correlates in a National Sample', Journal of Adolescent Health, 2009; 44:505–507.
[32] Watt L.D., Arnstein P. et al. 'Codeine for children: Weighing the risks', Nursing, 2013;63.

mother who had been inadvertently overdosing on codeine phosphate/paracetamol and paracetamol for six months. The infant developed hepatotoxicity. The infant displayed dependence on codeine phosphate/paracetamol and required treatment with morphine. After approximately six weeks in hospital, the infant was discharged.

During the referral review of codeine for pain relief in children the PRAC had previously recommended that, the use of codeine should be contraindicated in breastfeeding mothers. This contraindication is also considered applicable to breastfeeding mothers who use codeine-containing products also management of cough and/or cold as there is a risk of opioid toxicity to the breastfeeding child when the mother is using codeine and this risk is particularly high if the mother is an ultra-rapid metaboliser.

The PRAC recommended therefore, the contraindication of the use of these products in breastfeeding mothers. In addition, the PRAC considered that all codeine containing products, including those approved for adults and regardless of the indication, should have this contraindication in their labelling. Therefore, the PRAC suggests that National Competent Authorities of the EU Members States take the necessary actions to have the labelling of codeine products approved only for adults updated with this contraindication.

Conclusions on safety

The use of opioids in children entails a known risk of central respiratory depression. The safety profile of codeine raises greater concerns as codeine is metabolised to morphine at an unpredictable rate.

As discussed in section 2.2.1 of this assessment report, codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite.

If a patient has a deficiency or is completely lacking this enzyme an adequate therapeutic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of morphine toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.

Children who are CYP2D6 ultra-rapid metabolisers, even within recommended doses can develop morphine toxicity[33,34,35](Ciszkowski et al, 2009; Friedrichsdorf et al, 2013; Kelly et al, 2012). A review of serious and fatal cases in paediatric patients from the literature, global pharmacovigilance databases and regulatory authorities suggests that the respiratory depressant effects of codeine may influence the occurrence of respiratory complications. The risk of opioid toxicity is especially pronounced among ultra-rapid metabolisers due to its serious consequences of respiratory depression.

In total, fourteen reports of codeine intoxication in children related to the treatment of cough and respiratory infection were identified in the published literature. A review of these cases indicated that, four cases had a fatal outcome. The remaining cases were all life-threatening but resulted in full recovery. The children's age ranged from 17 days to 6 years.

[33] Ciszkowski C., Madadi P., Phillips M.S., Lauwers A.E., Koren G., 'Codeine, ultrarapid-metabolism genotype, and postoperative death', N Engl J Med, 2009;361(8):827-8.
[34] Friedrichsdorf S.J., Nugent A.P., Strobl A.Q. 'Codeine-associated pediatric deaths despite using recommended dosing guidelines: three case reports' *J Opioid Manag* 2013;9(2):151-155.
[35] Kelly L.E., Rieder M., van den Anker J., Malkin B., Ross C., Neely M.N., et al. 'More codeine fatalities after tonsillectomy in North American children', Pediatrics, 2012; 129:e1343-7.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal.

Codeine adverse drug reactions in paediatrics, as a result of opioid-induced toxicity, are a public health concern[36] (Madadi P, 2008). In addition to the key safety risk of ultra-rapid metabolism in certain patients with resulting life-threatening or fatal opioid toxicity and respiratory depression, codeine may also mask or delay treatment of a more serious underlying condition in children, and available data also highlighted a concern of codeine dependence and abuse in adolescents. There is also the risk of opioid toxicity in infants of breastfeeding mothers taking codeine.

As discussed in the previous referral procedure of codeine for pain in children, the PRAC recommended caution in the specific subpopulation of patients who might already have a compromised respiratory function. It is considered that with underlying breathing problems, the symptoms of morphine toxicity and respiratory depression may be increased. In view of these concerns, the PRAC concluded that codeine is not recommended for use in children whose breathing might be compromised.

The PRAC also considered that the risk of accidental overdose (four cases identified above) could be minimised by the use of child resistant containers (CRC). Therefore, the PRAC recommends child resistant containers (CRC) for all oral liquid codeine containing medicinal products.

2.3. Other information relevant to the assessment

2.3.1 Consultation of healthcare professional organisations

The PRAC also obtained additional information from European healthcare professionals' organisations (HCPO) on the paediatric population which could benefit from the use of codeine in the symptomatic treatment of cough and/or cold.

Overall, HCPOs were of opinion that there was no specific paediatric age group or condition that could benefit from the use of codeine as an antitussive. However, the use of codeine in cases of persistent irritating cough that is resistant to other antitussives was suggested.

It was also stated that there would be no detrimental impact if codeine was to be restricted in the paediatric population. Clinical experience did not demonstrate any known risks with alternative antitussives but the range of medications used (including unconventional and herbal medications) is very wide and these medications may have associated concerns.

2.3.2 Consultation of the Paediatric Committee (PDCO)

The PDCO was consulted in order to obtain additional information on the use of codeine-containing products in paediatric patients.

The PDCO, supported by majority, had the view that the benefits of codeine as an antitussive in children and adolescents are unclear, and no paediatric population or group could be defined where codeine as an antitussive would be considered as an essential therapeutic option. The PDCO acknowledged that the data demonstrating the efficacy of codeine as an antitussive in children are

[36] Madadi P., Koren G., 'Pharmacogenetic insights into codeine analgesia: implications to pediatric codeine use', Pharmacogenomics, 2008; 9(9),1267-84.

weak and therefore it is considered that there is not enough evidence to support codeine use in any paediatric patient group.

Additionally, it was highlighted that cough associated with upper respiratory tract infections is the dominating cause of cough in children. The large majority of childhood respiratory infections with cough are caused by viral infections, which are self-limiting and only lasting for a few days. In such clinical settings, it is not expected that codeine use brings any significant benefit, while the risks identified can be of serious consequences.

The PDCO by majority, considered that there would be no significant detrimental impact for paediatric patient care if the use of codeine in the cough indication was restricted to adults only. The Committee stated that there are fewer risks recognised with the use of alternative antitussives than with codeine used as an antitussive, in the paediatric population.

Codeine has an unpredictable therapeutic profile and may cause opioid intoxication in 'CYP2D6 ultra-rapid metabolisers'. Furthermore, it was pointed out that the variability in CYP2D6 genetic polymorphism and developmental changes during childhood put children at higher risk of opioid toxicity compared with adults. However, it was highlighted that data concerning safety of alternative antitussive medications should be taken in consideration.

The PDCO strongly indicated that codeine has a potential for abuse and dependence (in particular amongst adolescents) which could influence the drug's overall benefit-risk for the paediatric population. The Committee noted that OTC availability of codeine whether for pain or cough increases the risk of potential abuse and dependence, and commented that codeine-containing products should be subject to medical supervision..

2.3.3 EMA study on prescribing of codeine to children and adolescents for cough and/or cold

The EMA has performed a drug utilisation study (DUS) using IMS Health and THIN electronic health records and Nordic registries. The present analyses primarily concern the utilisation of codeine in children and were performed in the THIN database (UK general practice) and IMS database (general and paediatric practice in Germany, general practice in France). In addition, available on-line Nordic prescription registries have been queried. The study also analyses the incidence of death occurring within a short time span of a codeine prescription.

The proportion of prescribing of codeine related to cough varies significantly between countries. In Germany and Denmark the prescribing is predominantly defined as for cough. In France also a large proportion of the use is for cough. In Norway, Sweden and the UK prescribing for cough only accounts for a very small proportion.

The prescribing of codeine increases with age in all countries analysed even if at a different degree. In Germany the increase is lower due to the higher proportion of codeine prescribed against cough.

In the three countries where an analysis over-time was conducted, a small increase in prevalence for both codeine and codeine prescribed for cough is observed in France until 2011, while a decrease is observed in Germany and the UK. The UK showed the sharped decrease, driven by the decline of prescribing of codeine for cough in the younger group (0 – 11 years).

2.4. Risk minimisation activities

The PRAC, having considered the data submitted in the application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product: changes to the product information and child resistant containers should be recommended for all oral liquid codeine medicines to avoid accidental ingestion.

2.5. Overall benefit/risk assessment

Cough is a reflex response to mechanical, chemical, or inflammatory irritation of the tracheobronchial tree. Cough serves as a physiologic function to clear airways of obstructive or irritating material or to warn of noxious substances in inspired air.

Cough associated with upper respiratory tract infections (URTIs) is the dominating cause of cough in children. The frequency of acute URTIs is also age-related and occurs more frequently in children than in adults. The large majority of childhood respiratory infections with cough are caused by viral infections, which are self-limiting and only lasting for a few days. International guidelines have stated that cough associated with these conditions may be satisfactorily managed with fluids and increased ambient humidity. In the case of chronic cough, treatment should be directed at the underlying disease[24,11] (American Academy of Paediatrics Committee on Drugs 1997, American Academy of Paediatrics, AAP publications retired or reaffirmed 2006).

Codeine suppresses the cough reflex through a direct effect on the cough centre in the medulla. However, there is little clinical data in the medical literature to support the efficacy of codeine in the symptomatic treatment of cough and/or cold as current evidence does not find codeine to be more effective than placebo for acute cough in children.

The PRAC reviewed all data available from clinical trials, observational studies, meta-analyses, post-marketing data and further published data on the use of codeine containing products in children for treatment of cough and/or cold. The PRAC also considered data from the European Pharmacovigilance database (Eudravigilance), a drug utilisation study of the patterns of prescription of codeine. Moreover the PRAC consulted European healthcare professional organisations and the Paediatric Committee (PDCO).

Overall, only four published studies investigating the use of codeine-containing medicines for the treatment of cough in children could be identified. Two studies[17,18] (Kelly and colleagues, 1963 and Jaffe et al, 1983), which did not include a placebo control group, suggested that efficacy was no greater for codeine than the other antitussives but that the incidence of side effects in the codeine group was higher than in the comparator group. A randomised clinical trial (Jaffe G et al, 1983) and an epidemiological study (De Blasio F et al, 2012) did not show a significant effect of the treatment with codeine in cough and/or cold in children. In addition, another randomised clinical trial (Taylor et al, 1993) in children with codeine, dextromethorphan as an active comparator, and a placebo group show that neither codeine nor dextromethorphan were significantly better then placebo for the symptomatic treatment of cough in children under 12 years of age. In 2012, the Taylor et al study was included in a Cochrane review of non-prescription/over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings; this review additionally identified two randomised controlled trials where codeine was tested in adults[22,23] (Eccles R et al, 1992; Freestone C 1997): codeine was found to be no more effective than placebo.

Efficacy data is therefore limited, with no recent and well-established, controlled scientific studies to clearly support the benefit of codeine in the approved indications for cough and/or cold for the paediatric population.

Codeine is converted into morphine in the body by cytochrome P450 2D6 (CYP2D6), an enzyme which shows genetic polymorphism. Individuals are normally classified as poor (PM), extensive (EM) or ultra-rapid metabolisers (UM), depending on the activity of the enzyme. Whereas EMs or UMs are at risk of morphine toxicity, PMs may be at an increased risk of a lack of therapeutic effect. The unpredictable and variable metabolism of codeine in children, governed by CYP2D6 polymorphism, may cause some children to exhibit morphine-related serious adverse events such as breathing difficulties or respiratory depression even within the recommended doses. Therefore, this continues to represent a variable safety risk across all paediatric age groups.

A review of serious and fatal cases in paediatric patients from the literature, global pharmacovigilance databases and regulatory authorities suggests that the respiratory depressant effects of codeine may influence the occurrence of respiratory complications. The risk of opioid toxicity is especially pronounced among UMs due to its serious consequences of respiratory depression.

In total, fourteen reports of codeine intoxication in children related to the treatment of cough and respiratory infection were identified in the published literature. A review of these cases indicated that, four cases had a fatal outcome. The remaining cases were all life-threatening but resulted in full recovery. The children's age ranged from 17 days to 6 years. Data analyses from the Eudravigilance database identified a total of 50 case reports that could be related to opiate toxicity, of which 31 cases were in those younger than 6 years (including 4 fatal cases), 7 cases in older than 6 years and younger than 12 years (including 1 fatal case) and the remaining 12 cases were on those older than 12 and younger than 18 years (including 1 fatal case). Overall, the majority (38/50) of the cases were in patients younger 12 years of age and 6 were fatal cases. While acknowledging that uncertainties remain regarding the identification of particular paediatric populations at higher risk and the impact of age on codeine metabolism, the PRAC was of the opinion that neonates, toddlers and young children may be more vulnerable to opioid toxicity and therefore at special risk of life-threatening respiratory depression. The PRAC took into account that the enzymatic systems responsible for the metabolism of codeine in children older than 12 years of age can be considered comparable to that of adults.

The PRAC also noted that cough associated with upper respiratory tract infections is the dominating cause of cough in children. The large majority of childhood respiratory infections with cough are caused by viral infections, which are self-limiting and only last for a few days whereas in the case of chronic cough, treatment should be directed at the underlying disease[37,38] (American Academy of Paediatrics Committee on Drugs 1997, American Academy of Paediatrics, AAP publications retired or reaffirmed 2006). In such clinical settings, it is not expected that codeine use brings any significant benefit, while the risks identified can have serious consequences.

Based on all the above, the PRAC recommended the restriction of the use of codeine for cough and/or cold in the paediatric population. The PRAC considered that children below 12 years are at special risk of life-threatening respiratory depression and therefore, contraindicated the use of codeine in children below 12 years. The PRAC further considered that in children aged 12 years to 18 years for whom respiratory function might be compromised including those with neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive

[37] American Academy of Pediatrics Committee on Drugs 'Use of codeine- and dextromethorphan-containing cough remedies in children', Pediatrics 1997;99:918-20.
[38] American Academy of Pediatrics. AAP Publications Retired or Reaffirmed, October 2006. Pediatrics 2007;119(2):405.

surgical procedures, codeine is not recommended as these conditions may worsen symptoms of morphine toxicity.

In addition, the PRAC also recommended that the relevant risk minimisation measures from the previous referral[1] should also apply to the use of codeine in the symptomatic treatment of cough and/or cold. This included contraindication in patients of any age known to be CYP2D6 ultra-rapid metabolisers and in women of all ages who are breastfeeding. In this regard the PRAC noted that all codeine containing products approved for adults regardless of the indication, should have these contraindications included in their labelling. Therefore, the PRAC suggests that National Competent Authorities of the EU Member States to take the necessary actions to have the labelling of codeine products approved only for adults updated with the contraindications.

The PRAC also considered that the risk of accidental overdose (four cases identified) could be minimised by the use of child resistant containers (CRC). Therefore, the PRAC recommends child resistant containers (CRC) for all oral liquid codeine containing medicinal products.

2.6. Communication plan

The PRAC agreed on the following core communication elements for national communication, which should be considered by MAHs when agreeing a communication strategy with their national competent agency:

- Codeine is an opioid medicine that is widely used for relief of pain and is also authorised for the symptomatic treatment of cough and/or cold. [Insert information on national authorisation and legal status as needed]
- The main therapeutic effects of codeine are due to its conversion into morphine by an enzyme called CYP2D6. Some patients may convert codeine into morphine at a faster than normal (known as ultra-rapid metabolisers), resulting in high levels of morphine in the blood that can cause toxic effects such as breathing difficulties.
- The PRAC, in 2013, had reviewed the benefit-risk of products containing codeine for the relief of pain in children due to some fatal or life-threatening cases of morphine intoxication in children and introduced a number of risk minimisation measures to ensure that only children for whom the benefits are greater than the risks are given codeine for pain relief.
- Given that these risks may also apply to the use of codeine for the symptomatic treatment of cough and/or cold the PRAC subsequently started a review examining the benefits and risks of codeine when used in children for this indication.
- The PRAC has now finalised this review and has recommended that the use of codeine in children for the symptomatic treatment of cough and/or cold should be restricted as follows because of the safety concerns of morphine-like toxicity:
    - Codeine is contraindicated in children under 12 years of age;
    - Codeine is not recommended in paediatric patients aged 12 to 18 years of age with compromised respiratory function.
- In reaching these conclusions the PRAC notes that cough and/or cold is generally a self-limiting condition in children and adolescents and carefully considered the available data relating to safety and efficacy of codeine in the treatment of the cough and/or cold, the advice of the European Paediatric Committee and also clinical guidelines which recommend that persistent chronic cough in children should be treated based on aetiology.

- The PRAC also considered that although morphine-induced side effects may occur at all ages, the current evidence suggests that children below 12 years are at special risk of life-threatening respiratory depression with codeine. There also seems to be a particular risk in those paediatric patients of any age who might already have compromised respiratory function.
- The PRAC also concluded that the following recommendations that arose from the earlier analgesia referral should also apply to the use of codeine in the symptomatic treatment of cough and/or cold:
    - Codeine is contraindicated in patients of any age known to be CYP2D6 ultra-rapid metabolisers as the risk of morphine intoxication is extremely high in these patients.
    - Codeine is contraindicated in women of all ages who are breastfeeding due to an increased risk for the breastfeeding child when the mother is using codeine and she is an ultra-rapid metaboliser.

Clinicians should remain aware that patients may respond differently to codeine. Those caring for patients taking codeine should be advised to seek medical advice if symptoms of toxicity occur.

Symptoms of codeine toxicity include reduced levels of consciousness, somnolence, respiratory depression, 'pin-point' pupils.

2.7. Changes to the product information

Several sections of the summary of product characteristics (SmPC) have been amended to include the information of this review.

In section 4.2, Posology and method of administration, wording was added on the contraindication in children below the age of 12 years for the symptomatic treatment of acute cough and/or cold. A cross reference to section 4.3 was added.

Also the fact that codeine is not recommended for use in children aged 12 years to 18 years with compromised respiratory function for the symptomatic treatment of cough and/or cold was added to section 4.2. In this regard, in line with the previous referral on codeine for pain relief, a warning was included in the section 4.4., special warning and precautions for use, which list in detail conditions in which the respiratory function might be compromised (i.e. neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures).

Regarding Sections 4.3, 4.4 and 4.6 the PRAC was of the view that the previous contraindications, special warning and precautions for use and information introduced in the referral for pain relief in children, should also be applicable to all codeine medicinal products indicated for cough and/or cold in children. These were: the contraindications in women during breastfeeding and also in patients known to be CYP2D6 ultra-rapid metabolisers; warnings on CYP2D6 metabolism including a table listing the estimated prevalence of ultra-rapid metabolisers in different populations; information on breastfeeding women in section 4.6.

Administrative additions to section 4.8, in line with the recent QRD template were introduced.

The package leaflet (PL) was amended accordingly.

3. Conclusion and grounds for the recommendation

Whereas

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data for codeine containing medicinal products for the treatment of cough and/or cold in children.
- The PRAC considered available data on the safety and the efficacy of the codeine containing medicinal products for the treatment of cough and/or cold in children in relation to the risk of opioid toxicity. This included MAH responses, published literature data which became available since the initial granting of the marketing authorisations and consultation of healthcare professionals and other experts.
- The PRAC considered that there is limited evidence that support the efficacy of codeine in cough and cold and that these are generally self-limiting conditions. Treatment guidelines recommend treatment of persistent chronic cough in paediatric patients based on aetiology.
- The PRAC having reviewed the available evidence and in particular the risk of serious adverse reactions of opioid toxicity in children, the nature of the condition and the views of clinical experts considered that the use of codeine containing medicinal products for the treatment of cough and/or cold in the paediatric population is not recommended.
- In addition, the PRAC considered that the current evidence suggests that children below 12 years are at special risk of life-threatening respiratory depression and therefore, concluded that the use of codeine containing medicinal products for the treatment of cough and/or cold is contraindicated in children below 12 years. The PRAC further considered that in children aged 12 years to 18 years with compromised respiratory function the use of codeine is not recommended.
- The PRAC, in line with the restrictions introduced during the codeine referral for pain relief in children, also concluded that all codeine containing medicinal products for the treatment of cough and/or cold should be contraindicated in women when breastfeeding, as well as in patients known to be CYP2D6 ultra-rapid metabolisers.

Therefore, the PRAC recommends the variation to the terms of the marketing authorisation for medicinal products containing codeine for cough and/or cold in children referred to in Annex I, for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III of the PRAC recommendation.

The PRAC, as a consequence, concluded that the benefit-risk balance of the medicinal products containing codeine for cough and/or cold in children remains favourable, subject to the inclusion of the restrictions, warnings and other agreed changes to the product information.

4. Annexes

The list of the names of the medicinal products, marketing authorisation holders, pharmaceutical forms, strengths and route of administration in the Member States are set out Annex I to the opinion.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 April 2015
EMA/249413/2015

Codeine not to be used in children below 12 years for cough and cold

The CMDh[1] has agreed by consensus new measures to minimise the risk of serious side effects, including breathing problems, with codeine-containing medicines when used for cough and cold in children. As a result of these new measures:

- Use of codeine for cough and cold is now contraindicated in children below 12 years. This means it must not be used in this patient group.
- Use of codeine for cough and cold is not recommended in children and adolescents between 12 and 18 years who have breathing problems.

The effects of codeine are due to its conversion into morphine in the body. Some people convert codeine to morphine at a faster rate than normal, resulting in high levels of morphine in their blood. High levels of morphine can lead to serious effects, such as breathing difficulties.

The new measures follow a review by EMA's Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC considered that, although morphine-induced side effects may occur in patients of all ages, the way codeine is converted into morphine in children below 12 years is more variable and unpredictable, making this population at special risk of such side effects. In addition, children who already have problems with their breathing may be more susceptible to respiratory problems due to codeine. The PRAC also noted that cough and cold are generally self-limiting conditions and the evidence that codeine is effective at treating cough in children is limited.

In addition to the new measures for children, codeine must also not be used in people of any age who are known to convert codeine into morphine at a faster rate than normal ('ultra-rapid metabolisers') nor in breastfeeding mothers, as codeine can harm the baby because it passes into breast milk.

This review comes after a previous review of codeine for pain relief in children, which resulted in several restrictions being introduced in order to ensure that the medicine was used as safely as possible. As it was realised that similar considerations could apply to the use of codeine for cough and cold in children, a second EU-wide review of such use was started. The restrictions for codeine for cough and cold are largely in line with the previous recommendations for codeine when used for pain relief.

[1] The CMDh is a medicines regulatory body representing the European Union (EU) Member States, Iceland, Liechtenstein and Norway.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

As the CMDh has now agreed the PRAC measures by consensus, the measures will be directly implemented by the Member States where the medicines are authorised, according to an agreed timetable.

Information for patients

- Following an EU-wide review of codeine when used for cough and cold, changes have been made to the way the medicine is used to ensure that the benefits continue to outweigh the risks in children and adolescents.
- Codeine-containing medicines for cough and cold must not be used in children below 12 years of age because of the risk of serious side effects, including breathing problems.
- In children and adolescents between 12 and 18 years who have problems with their breathing, codeine is not recommended as this population may be more susceptible to breathing problems due to codeine.
- Patients of all ages who are known to be 'ultra-rapid metabolisers', which means that they convert codeine into morphine very rapidly, must not use codeine for cough and cold as they are more at risk of serious side effects with codeine.
- Mothers who are breastfeeding must not take codeine as codeine can harm the baby because it passes into breast milk.
- Parents and caregivers who notice any of the following symptoms in a patient given codeine should stop giving the medicine and seek medical attention immediately: slow or shallow breathing, confusion, sleepiness, small pupils, feeling or being sick, constipation and lack of appetite.
- If you or your child are being treated with codeine and have any questions or concerns about your treatment, speak to your doctor or pharmacist.

Information for healthcare professionals

- Codeine for cough and cold is now contraindicated in children below 12 years, and not recommended in children between 12 and 18 years with compromised respiratory function.
- Codeine is also contraindicated in women during breastfeeding and patients known to be CYP2D6 ultra-rapid metabolisers.

These new measures follow a review of available safety and efficacy data on codeine when used for cough and cold, including data from clinical studies, observational studies and meta-analyses, post-marketing data in Europe and other published literature on the use of codeine in children.

In total, 14 cases of codeine intoxication in children (aged from 17 days to 6 years) related to the treatment of cough and respiratory infection were identified in the published literature, four of which had a fatal outcome.

The available data indicate that the way codeine is converted into morphine in children below 12 years is more variable and unpredictable, making this population at special risk of morphine-induced side effects. In addition, the evidence that codeine is effective at treating cough in children is limited and international guidelines emphasise that cough associated with viral infections may be satisfactorily managed with fluids and increased ambient humidity; in the case of chronic cough, treatment should be directed at the underlying disease.

More about the medicine

Codeine is an opioid medicine that is converted into morphine in the body. It is widely used for pain relief and for the treatment of the symptoms of coughs and colds. In the EU, codeine-containing medicines have been approved via national procedures, and are available either on prescription or over the counter in the different Member States. Codeine is marketed as a single-ingredient medicine or in combination with other active substances.

More about the procedure

The review of codeine when used for cough and cold in children was initiated in April 2014 at the request of the German medicines agency (BfArM), under Article 31 of Directive 2001/83/EC.

The review was carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), EMA's Committee responsible for the evaluation of safety issues for human medicines, which has made a set of recommendations. As codeine-containing medicines are all authorised nationally, the PRAC recommendations were forwarded to the CMDh for its position. The CMDh is a body representing EU Member States as well as Iceland, Lichtenstein and Norway, and is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.

On 22 April 2015 the CMDh adopted its position by consensus, so the measures recommended by the PRAC will be directly implemented by the Member States where the medicines are authorised, according to an agreed timetable.

Contact our press officer

Monika Benstetter

Tel. +44 (0)20 3660 8427

E-mail: press@ema.europa.eu

DIVISION OF NONPRESCRIPTION DRUG PRODUCTS CONSULTATION

Date:	November 12, 2015
To:	Sally Seymour, MD Division of Pulmonary, Allergy and Rheumatology Products
From:	Benjamin Bishop, PharmD Division of Nonprescription Drug Products (DNDP)
Through:	Valerie Pratt, MD DNDP
	Theresa Michele, MD DNDP
Subject:	Codeine-containing products regulated under the OTC drug monograph

Regulation of Over-the-Counter Drugs

Over-the-counter (OTC) drugs may be regulated by FDA under one of two processes:

- The NDA (for new drugs) or ANDA (for generic drugs) process as described in 21 CFR Part 314
- The OTC drug monograph process described in 21 CFR Part 330
    - OTC Drug Review (ingredients on the market prior to 1972)
    - Time and Extent Application ("new" ingredients after 1972)

In the U.S, all OTC codeine containing products are currently regulated as OTC drugs under the OTC drug monograph process. Monograph products may be sold under without product-specific pre-market approval as for a new drug application (NDA) or abbreviated new drug application (ANDA). Table 1 compares features of the NDA and monograph processes. It is followed by details of each regulatory process.

Table 1: OTC Drugs Regulatory Pathway

New Drug Application	Monograph Process
• Product-specific (including formulation) • Confidential filing • Clinical development required • Application submitted for approval • Application fees (Prescription Drug User Fee Act) • Mandated timelines • Potential for marketing exclusivity • Reporting requirements • Comply with good manufacturing practices	• Ingredient- and category-specific regulations (CFR 330-358) • Public process - No data confidentiality • No clinical development • No FDA application or pre-approval • No user fees • No mandated timelines • No potential for marketing exclusivity • Limited reporting requirements (serious adverse events) • Comply with good manufacturing practices

In the sections that follow, the most important differences to note are that, compared to a drug approved via the NDA process, products marketed under the monograph system: (1) do not undergo FDA review of the final product, (2) do not undergo FDA review of formulation or manufacturing changes, and (3) changes to the monograph to accommodate new ingredients or other condition of use, scientific advances, new safety information, etc. require a lengthy "rulemaking" process, which we will describe.

The NDA Process

The purpose of the NDA process is to demonstrate that a specific final formulation drug product is safe and effective for use as directed in its approved labeling, based on safety and effectiveness data contained in the NDA. FDA must review the NDA and approve the drug for marketing before the product can be sold legally in the U.S., and most changes to the product's formulation, manufacturing process, or other approved specifications must also be reviewed and approved before they are introduced. There are currently no codeine products approved for OTC use under the NDA process.

The Monograph Process

In contrast to the NDA process, pre-marketing review by the FDA is not required for OTC drug products that meet the standards established in an applicable OTC drug monograph. A monograph is a FDA regulation that serves as a kind of "rule book" for formulating OTC products by specifying the "conditions of use" under which a given category of products (such as sunscreens) are considered to be "generally recognized as safe and effective" (GRASE).[1] In addition to identifying acceptable active ingredients (and their allowed concentrations), GRASE conditions of use can include features such as dosages, route of administration, labeling, and in some cases such as sunscreens, final formulation efficacy testing.[2]

In response to the 1962 amendments to the Federal Food, Drug, and Cosmetic Act (FD&C Act) which required more robust approval standards for drugs, including demonstrating efficacy, FDA initiated a scientific review of the active ingredients that were in marketed OTC drug products to evaluate their safety and effectiveness. This review, established in 1972, is called the OTC Drug Review, which results in the establishment of OTC drug monographs for each therapeutic category. The use of regulatory monographs rather than product-by-product review and approval was considered necessary because there were so many OTC products already on the U.S. market (~800 active ingredients and 1,400 uses of over 100,000 products). The overall framework established in 1972 provided that contracted "advisory review panels" (distinct from the advisory committees of today) would initially review the safety and effectiveness of the active ingredients, and the labeling and other aspects of OTC products that were then or previously marketed in the United States to determine whether each could be classified as generally recognized as safe and effective (GRASE) for use in self-treatment, and to draft class-based recommended monographs for FDA's consideration. The progression from a panel's recommendations to FDA's establishment of a final OTC monograph requires multi-step public rulemaking proceedings, with publication in the Federal Register and opportunity for public comment at each step. Because products were already on the market prior to 1972 when the OTC Drug Review was established, these products are allowed to remain on the market during the rulemaking process until a final rule issued that establishes an ingredient as not GRASE.

---

[1] Drugs that are GRASE fall outside the statutory definition of a "new drug," 21 U.S.C. 321(p), and therefore do not require NDA approval before marketing as 21 U.S.C. 355(a) would otherwise require.

[2] In addition to complying with the terms of an applicable monograph, OTC drugs marketed under the monograph process must also comply with drug registration and listing requirements, current good manufacturing practices, and other applicable labeling requirements.

Codeine in OTC Monographs

There are three codeine active ingredients discussed in the OTC monographs: Codeine, codeine phosphate, and codeine sulfate. Codeine was evaluated by the OTC drug review in the antitussive and internal analgesic sub-categories. However, only the antitussive category included codeine as GRASE. Therefore, codeine and these two common salts are only permitted in the Final Monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use, which includes the antitussive sub-category. Although these products are labeled for OTC use under the monograph, the rulemakings also established professional labeling for some uses under the monograph. Professional labeling under the monograph is intended for use by health care professionals but does not require a prescription.

For the internal analgesic monograph, the review panel recommended that codeine be classified as non-GRASE (nonmonograph) and FDA agreed. FDA published this finding as a proposed rule in 1992 and a final rule in 1993 establishing that codeine, codeine phosphate and codeine sulfate are not GRASE and are misbranded when marketed OTC under the monograph with an indication for pain [21 CFR 310.545(a)(23)(i)].

The Antitussive Monograph

The OTC drug review of the antitussive subcategory resulted in the classification of codeine as a Category I (GRAS/E) antitussive agent. Codeine, along with codeine phosphate and codeine sulfate, is currently listed as an antitussive active ingredient in 21 CFR 341.14(a)(2). It is important to note that these codeine ingredients may be used only in combination with at least one nonnarcotic active ingredient as stated in 21 CFR 290.2 and 21 CFR 1308.15, which also limits the concentration of codeine in such combinations and requires that the nonnarcotic ingredient confer “valuable medicinal qualities other than those possessed by codeine alone.” The regulatory history is described in the following paragraphs.

Advance Notice of Proposed Rulemaking (ANPR), 9 September 1976

The Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use (CCABA) Panel report was published in the Federal Register on 9 September 1976, along with FDA comments and a proposal for categorization of the reviewed agents, including codeine preparations. The FDA concurred with the recommendation that the three codeine active ingredients be categorized as GRASE.

Prior to the ANPR, on 12 September 1972, the FDA issued a proposed regulation (37 FR 18741) to require a prescription for cough preparations containing codeine. This action came at the request of the Drug Enforcement Agency (DEA) and the FDA asked

the CCABA Panel to review the available data with representatives from both the DEA and FDA. After review, the Panel concluded that codeine and its salts are safe and effective for OTC use as antitussives when used in accordance with instructions on the label, and viewed the potential for abuse as negligible. The Panel also forwarded a statement to the FDA Commissioner in which the Panel recognized that considerations go beyond questions of safety and effectiveness alone, but that the Panel did not deem it part of its function to evaluate other factors. As a result, the FDA withdrew the proposed regulation on 24 March 1975 (40 FR 12998), thus retaining the OTC status of codeine in cough preparations.

The 1976 ANPR also included the Panel's general discussion of antitussives, described in Section III of the Panel Report. The data reviewed for codeine preparations led the Panel to recommend a Category I classification. At the time of the review, codeine was noted for its high level of efficacy and low abuse potential. In the proposed rule:

> Part 341.14(a) listed the permitted active ingredients codeine, codeine alkaloid, codeine phosphate, and codeine sulfate, along with the permitted dosages for adults and children ages 2 and older.
>
> Part 341.40 listed the permitted combinations of active ingredients, and allowed the combination of codeine with antihistamines, bronchodilators, expectorants, and nasal decongestants.
>
> Part 341.74 listed the permitted indications for antitussives: "Cough suppressant which temporarily reduces the impulse to cough," with several variations in wording. Codeine preparations were also permitted the indication "Calms the cough control center and relieves coughing."
>
> Part 341.90 listed several statements permitted in professional labeling but none of these referred to codeine.

Proposed Rule, 19 October 1983

FDA issued a notice of proposed rulemaking in the form of a tentative final monograph (TFM) that would establish conditions by which OTC antitussive drug products are GRAS/E and not misbranded.

FDA received two comments regarding codeine's OTC status which were evaluated and considered in the TFM. One comment stated that codeine-containing products should be available OTC due to the high cost of obtaining a prescription, while another disagreed with the OTC status of codeine because the abuse potential was too high. FDA maintained its proposal that codeine be considered GRAS/E for OTC use as an antitussive agent under current DEA and state restrictions.

FDA also received two comments from pediatricians objecting to the use of codeine in children. FDA requested a recommendation from the American Academy of Pediatrics, which responded with a report stating: "We believe there is a preponderance of

evidence that codeine-containing cough syrups can be hazardous to young children, even in prescribed doses." FDA decided to propose that a codeine dose for children ages 2 to less than 6 be provided in professional labeling only, and that OTC labeling state "consult a doctor" for this age group. FDA also invited specific comment on this proposal.

Final Rule, 12 August 1987

FDA issued a final rule in the form of a final monograph after considering public comments on the proposed TFM and all new known data. One comment requested clarification of the professional labeling requirement concerning the distribution of a calibrated dispensing device. FDA responded by revising the professional labeling to include the following statements:

> Parents should be instructed to obtain and use a calibrated measuring device for administering the drug to the child, to use extreme care in measuring the dosage, and not exceed the recommended daily dosage.
>
> A dispensing device (such as a dropper calibrated for age or weight) should be dispensed along with the product when it is intended for use in children 2 to under 6 years of age to prevent possible overdose due to improper measuring of the dose.

FDA also revised the OTC labeling directions to include the following statement:

> Adults and children 12 years of age and over: Oral dosage is 10 to 20 milligrams every 4 to 6 hours, not to exceed 120 milligrams in 24 hours, or as directed by a doctor.

Current Federal Regulations on Codeine Products as a Controlled Substance

Codeine is designated as a Schedule V controlled substance, and FDA established the maximum concentrations of codeine permitted in combination with other non-narcotic active medicinal ingredients.

21 CFR 1308.15(c) Narcotic drugs containing non-narcotic active medicinal ingredients

> Any compound, mixture, or preparation containing any of the following narcotic drugs, or their salts calculated as the free anhydrous base or alkaloid, in limited quantities as set forth below, which shall include one or more non-narcotic active medicinal ingredients in sufficient proportion to confer upon the compound, mixture, or preparation valuable medicinal qualities other than those possessed by narcotic drugs alone:
>
> 1. Not more than 200 milligrams of codeine per 100 milliliters or per 100 grams.

2. Not more than 100 milligrams of dihydrocodeine per 100 milliliters or per 100 grams.

FDA issued a final rule on 01 February 2002 (67 FR 4904) to amend regulations regarding certain label statements on prescription drugs. Section 290.1 was added to make clear the agency's determination that a controlled substance in Schedules II-V of the CSA must be dispensed by prescription only unless otherwise determined by the agency. Section 290.2 was then added to allow the exemption for small amounts of codeine defined as not more than 200 milligrams of codeine per 100 milliliters or per 100 grams.

21 CFR 290

Sec. 290.1 Controlled substances

> Any drug that is a controlled substance listed in schedule II, III, IV, or V of the Federal Controlled Substances Act (CSA) or implementing regulations must be dispensed by prescription only as required by section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act unless specifically exempted in 290.2. [67 FR 4906, Feb. 1, 2002]

Sec. 290.2 Exemption from prescription requirements

> The prescription-dispensing requirements of section 503(b)(1) of the Federal Food, Drug, and Cosmetic Act are not necessary for the protection of the public health with respect to a compound, mixture, or preparation containing not more than 200 milligrams of codeine per 100 milliliters or per 100 grams that also includes one or more nonnarcotic active medicinal ingredients in sufficient proportion to confer upon the compound, mixture, or preparation valuable medicinal qualities other than those possessed by codeine alone. [67 FR 4907, Feb. 1, 2002]

Codeine Availability

A 2015 review by FDA found 45 products currently registered with FDA to be marketed under the OTC monograph. Two unapproved New Drug products were also found, and additional products may have been marketed previously and subsequently withdrawn, or not registered. The registered products comprise 13 distinct combinations of codeine with various other active ingredients, and were registered by 18 different companies.

The utilization data show declines in both OTC and outpatient retail pharmacy prescription codeine product-related measures. Compared to year 2010, U.S. retail OTC sales of codeine-containing cough and cold products decreased 85%, to 169,000 bottles/packages in 2014. From 2010-2014, the number of pediatric patients (0-18 years old) receiving dispensed prescriptions for any codeine-containing product

decreased 40% to 1.9 million patients; of which, 56% were <12 years old and 45% were 12-18 years old. By drug class, 76% of these pediatric patients received analgesic codeine-containing products and 26% received codeine-containing cold/cough products in 2014.

Twenty-eight states and the District of Columbia permit the sale of codeine without a prescription, while 22 states and Puerto Rico prohibit the sale of codeine without a prescription.[i] Most if not all of the state laws allowing the OTC sale of codeine require the pharmacist to oversee or personally complete the transaction, and allow the pharmacist to choose not to sell the product OTC. For codeine that is sold OTC, all states require that the purchaser's identifying information and details of the sale be recorded. States differ on the maximum allowable quantity which can be purchased at one time (60 mL to 240 mL), the amount of time required before additional purchases are permitted (48 hours to 96 hours), and the minimum age of a purchaser (18 years to 21 years). The variations between states involve regulations and laws which are more restrictive than the federal requirements in 21 CFR 1306.26.

[i] National Association of Board of Pharmacy: The 2015 Survey of Pharmacy Law. 2015; 73-77.